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CATARRHAL JAUNDICE, SPORADIC AND EPIDEMIC, AND ITS RELATION TO ACUTE YELLOW ATROPHY OF THE LIVER

By E. A. COCKAYNE

Historical.

Catarrhal jaundice was well known to Greek and Roman writers, and is mentioned in the *De internis affectionibus*, often attributed to Hippocrates, as the fourth kind of jaundice. *Ἄλλος ἴκτερος. ἐπιδήμιος οὗτος καλέεται, διότι πᾶσαν ὥρην ἐπιλαμβάνει, γίγνεται δὲ ἀπὸ πλησμονῆς μάλιστα καὶ μέθης ἐπειδὰν ῥιγώσῃ.*

The writer after this description of its etiology and frequency, which is still commonly accepted, goes on to say that it is usually accompanied by slight fever, but is soon cured. In the Epidemics, Books I and III, jaundice in epidemic form is mentioned, but the description is evidently that of relapsing fever in one and the same disease or malaria in the other.

The first undoubted reference to catarrhal jaundice in epidemic form is that of Cleghorn, who writes of its prevalence in Minorca in 1745. Epidemics were noted along the Ligurian coast from January to March 1793, at Ludenscheid in the county of Mark from August to November 1794, and at Greifswald from November 1807 to February 1808. These with others occurring in subsequent years are mentioned by Hirsch. In the British Isles there was an epidemic in 1852 almost confined to children living in Birmingham or the neighbourhood and lasting from September to November. Montagu Champneys describes one from East Sussex in 1861, which affected eighteen individuals of all classes and included members of the families of the Vicar and M.F.H., whose ages ranged from 8 to 17. There was an extensive epidemic, in which at least 300 people were affected, at Rotherham in 1863 in which both children and adults were attacked, and there have been many small outbreaks in all parts of the country in later years, especially numerous in 1894, 1901, and 1911. The disease was very common in America amongst the Federal troops in the war between North and South, and there were 22,569 cases with 161 deaths amongst a total of 2,218,559 men; and in South Africa in the Boer War from February to June (autumn and winter months) there were 5,648 cases, with a very small but unknown mortality.

In the autumn of 1870 it was common amongst the civilians and troops in

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Paris, and from February to May, amongst the Bavarian troops stationed to the south-west of Paris, there were 799 cases amongst 33,380 men. In 1871 to 1872 it was again common in Paris. It is of fairly frequent occurrence amongst French and German troops.

It appears, indeed, to have a very wide geographical range, and though records from tropical countries are rare, it is not unlikely to be overlooked in those regions owing to the prevalence of more important diseases which also cause jaundice, such as yellow fever, relapsing fever, and malaria. Undoubted epidemics have been recorded in Europe from the British Isles, France, Germany, Austria, Russia, Norway, Sweden, Denmark, Holland, Switzerland, Italy, and Greece; in Asia, from Smyrna and various parts of India and Japan; in Africa, from Egypt and South Africa; in America, from numerous places in the Northern half of the continent, and from Martinique in the West Indies; in Australia, from Victoria and New South Wales. These epidemics have varied greatly in severity in different localities and in the same locality at different times, and it is almost certain that two diseases or groups of diseases different in etiology have been described under the title of epidemic or infectious catarrhal jaundice, though it must be admitted that Costa and Chauffard consider them to be all one, and Hunter thinks this probable. The first of these, and the rarer, was described by Weil in Germany in 1886, and his name is usually applied to it, but details of epidemics of the same kind had been published in France by Lancereaux in 1882 as 'Ictère grave essentiel', by Landouzy in 1883 as 'Fièvre bilieuse' or 'typhus hépatique bénin', and by Mathieu in 1886 as 'Ictère fébrile à rechutes'. In Germany it has been called Biliöse Typhoid, Icterus typhosus, and Typhus biliosus nostras.

Description of the Disease.

This disease, though, like all infectious diseases, it is somewhat variable, commences as a rule with fever, headache, severe pains and tenderness in the muscles of the legs and to a less degree in other muscles, nausea and vomiting. Diarrhoea is sometimes found, but more commonly there is constipation. There is tenderness over the liver, enlargement of the spleen, albumin in the urine in more than half the cases, and casts also are frequently present. Jaundice usually appears early, as the temperature begins to fall, is often slight, and does not last long. Epistaxis is common, as are petechiae under the skin, and less frequently haemorrhages from the stomach, intestines, lungs, ears, and gums are met with, and haematuria is a rare accompaniment. The fever often lasts eight to ten days, and there may be a further rise of temperature for three to five days later, though the percentage of cases in which this is seen varies much in different epidemics. Quincke gives 40 per cent. and Tymowski 22 per cent. Young adults, especially butchers, soldiers, and sewermen, are usually attacked in the European outbreaks. Epidemics are most common in the summer from May to October, and it is apt to recur in the same place in different years.

The etiology of the disease is not satisfactorily settled, but there is evidence that some epidemic cases and a few other sporadic ones with similar symptoms have been due to the bacillus proteus fluorescens. Jaeger found this organism in the water in which his patients had bathed, and in the urine and internal organs of such of his patients as died, and less commonly in the blood. It was also present in ducks which were dying of jaundice on the same water. The same bacillus has been isolated in cases of this character by Weil, Brooks, Libman, and Satterlee. Other organisms found have no claim to specific character. In others, where no organism has been found, or where none has been looked for, there has been evidence that the disease has been due to contaminated food or water. The negative results obtained by Sandwith in Smyrna and Valassapoulo in Alexandria, the two places where the disease is most common, and where careful bacteriological examinations have been made, suggest that the bacillus proteus has only been the cause of isolated outbreaks, even if it be capable of producing infectious jaundice at all, and that the causal agent may be still unknown. Worms described an epidemic at St. Cloud in May, 1865. The onset was sudden and accompanied by great prostration. Epistaxis and petechiae in the skin were noticed, and jaundice usually followed the onset in two days. Forty-nine were affected, twenty-three more or less gravely and eight with great severity. In these haemorrhage occurred from the ears and gums, and there was albumin and epithelial débris in the urine. Parotitis occurred in one case. The epidemic was attributed to drinking water taken from a reservoir contaminated with putrefying animal matter, and ceased as soon as this was no longer used. Carville describes another in the garrison at Gaillon in 1859. There were 47 cases with 11 deaths; epistaxis was met with in 15, purpura in 3, and haematemesis in 1, and all had albuminuria. The incubation period was six days. In 1877 an epidemic at Lille, described by Arnould and Coyne as Ictère Grave, resulted in four deaths out of ten cases. The liver, at first enlarged in all, was observed to diminish in size in fatal cases as the disease progressed. In one it weighed only 850 grammes instead of the average 1900 grammes. The liver was shrunken and yellow with rhubarb-coloured areas, and exactly resembled the appearance met with in acute yellow atrophy. The urine contained traces of albumin, but no casts or epithelial débris. Haemorrhages were common; haematemesis was seen in six, three of whom recovered, bleeding from the gums in two, and epistaxis in one. The skin showed a condition of ecchymotic lividity. Jaundice appeared early. Sandwith, under the name 'infectious jaundice', has given an account of a form epidemic and endemic at Smyrna, which is probably the same disease. Epidemics occur from April to October. There is a primary fever lasting three to five days and then jaundice lasting seven to nine days, followed in three-quarters of the cases by secondary fever lasting a further period of seven to nine days.

The incubation period is only two days. There is a sudden onset with rigor and headache, and a temperature of 102° to 104° F. is generally reached. Jaundice appears in three or four days, and is accompanied by tenderness and enlargement of the liver; but in some cases it may be very slight or even absent.

The spleen is enlarged. The urine is scanty and highly coloured, and contains a trace of albumin in the first stage; in the second there is more albumin, blood and casts appear, and the urine becomes still more scanty. Later on, the seventh or ninth day, a remarkable urinary crisis occurs, first investigated by Kelsch, in which there is polyuria and excessive excretion of urea takes place. The nervous symptoms are headache, giddiness, sleeplessness, muscular twitchings, and muscular pains at the nape of the neck and calves of the legs, with tenderness on pressure in the same situations. Nausea and vomiting appear early and constipation is the rule, though diarrhoea may be present in the most severe cases.

The stools become clay coloured or white after the jaundice is established. Epistaxis and intestinal haemorrhages may be present, haematemesis is found in 2 per cent.; bleeding from the gums and haemoptysis are sometimes seen, and more rarely haematuria. Petechial haemorrhages in the skin are very frequent. The death-rate varies from 10 to 60 per cent. The same disease with a death-rate averaging 32 per cent. is described by Valassapoulo in Alexandria, where it is prevalent every year from April till the winter. Those classes are affected who live in the lowest and most insanitary quarters near to where the sewage escapes into the sea. The jaundice appears rather later, thirteenth to fifteenth day, and the kidneys are less affected. There is no actual nephritis seen post mortem, though in life symptoms of renal insufficiency are met with. Parotitis is common. In the fatal cases the liver is enlarged in those who die early, but smaller than natural in those who die later in the disease. In those who died with only slight jaundice the gall-bladder was found empty, but in deeply jaundiced cases was full of thick dark bile. The liver showed fatty degeneration and a diffuse hepatitis with leucocytic infiltration near the portal spaces. Many organisms were found, but none appeared to be specific. Valassapoulo attributes the disease to infected food or water, and found it most common in the bazaars, where the sewers are too stagnant and where organic matter readily decomposes. Sandwith thinks that it is due to an alimentary infection, or possibly to the bite of some insect, and is certainly not conveyed directly from person to person. In Nauplia, where it was formerly epidemic, it has disappeared since the drainage was improved. Primarily it only affects the lowest classes and is essentially a filth disease. The disease is probably endemic round the shores of the Mediterranean, being met with in Egypt, Asia Minor, Constantinople, Greece, Dalmatia, the Ionian Isles, Malta, and epidemics of milder character are met with in Italy, Germany, Russia, and France. It has been described from China, from Pekin and Tientsin. The small epidemics recorded in England under this name are catarrhal and not infectious jaundice.

Epidemic Catarrhal Jaundice.

Found over a much wider area, and in many respects contrasting with infectious jaundice or Weil's disease, is another and much milder disease, true

epidemic catarrhal jaundice, and to this form most recorded epidemics of jaundice belong. These vary considerably in character, so that in the most severe they may be very like the milder forms of Weil's disease, but generally they are easily distinguishable from it.

Epidemic catarrhal jaundice is decidedly more common in the autumn, winter, and spring, though it may occur at any time of year.

The etiology is very obscure. Many organisms have been described, but none have proved to be specific. In some epidemics both the blood and the internal organs have proved to be sterile and harmless when injected into animals. All classes are equally affected. Children are much more frequently attacked than adults, and many small outbreaks affect them alone; and this has happened in some of the larger ones, too, such as the Birmingham epidemic of 1852, in which the ages ranged from 1½ to 10 years. In the Moscow epidemic described by Kissel and the Dresden epidemic by Meinert the majority of those affected were under 15. In the Derbyshire epidemic more occurred between 20 and 30 than at any other ages, and in the Bolton epidemic affecting 150 people the majority were between 17 and 25; in the Basle epidemic, lasting from August 1874 to March 1875, and affecting 200 people, 36 were under 13 years of age and 163 between 15 and 30. Others, especially in barracks and gaols, are confined to adults, but young recruits are the chief sufferers. In the Bloemfontein epidemic in 1901 adults alone suffered, and the majority of cases occurred in young men. Costa mentions an epidemic in which old soldiers, who were isolated from the recruits by their different training, were the only ones who contracted the disease, but this is quite exceptional. Infants usually escape, but undoubted cases have been described at the age of 2, 3, and 4 weeks and many under 12 months. The age at which children are most susceptible is from 4 to 12 years. Old people are seldom attacked, but cases have been noticed in the larger epidemics in people aged 50, 55, 57, 60, and 68 (Meinert), 60 (Vaisey), 73 (Hagenbeck), three between 60 and 70, and one between 70 and 80 (Plowright, King's Lynn).

There is strong evidence that, unlike infectious jaundice, it is not spread by means of food or water, but is an air-borne disease. Costa describes with great care an epidemic in soldiers, in which the disease spread in spite of drinking water being no longer permitted, tea and other substitutes being used, and which extended to regiments whose food and drinking water came from a different source. Even after the troops had been removed to a different part of the country the epidemic still continued. Viguier, who made a careful study of an epidemic beginning in June at Verdun, found that it was confined to one battery, though water and food were common to all the garrison. All the cases were very mild, some febrile and some afebrile. Symptoms of gastro-enteritis were very slight. He considered that no method of dissemination was possible but a direct one from man to man, and that the degree of infectivity was low.

The cases occurred in groups around those who fell ill first, and the original source of the disease was thought to be infected earth inhaled by the men at

work on a trench, and then swallowed. In England it has been noticed that two or more villages may be affected, and in such cases each probably has its own local water supply. Peck in the Derbyshire epidemic of August and September, 1901, showed that food and water were not the cause. Sixty-nine people were affected living in two villages supplied by moorland reservoirs. One man already infected travelled to Flintshire and there passed on the disease to three others.

Kershaw at Bolton in 1901 noticed that cases usually arose in the neighbourhood of previous ones, and that some districts remained quite free.

Vaisey in a rural epidemic showed that it spread from one village to another three miles away, carried by a child aged 8, who had mixed with affected children in the first village and who contracted the disease.

Dr. Fowler of Ellon tells me that in East Aberdeenshire, where small epidemics are not uncommon, it spreads irrespective of water supply, and I am indebted to him for details of an epidemic which took place in the autumn of 1911 in Ellon and its neighbourhood. Children attending three schools, Braeside School, Savoch, Arnage and Esslemont, were affected, the greatest number at Esslemont; and all three schools have an entirely different water supply. Most of the houses where the children live have their own local supplies, and it is impossible to incriminate either food or water. The steady spread of the disease in the larger epidemics of which full details are available, such as those at Eudes, Hanau, and in the kingdom of Saxony, seem to indicate that personal contact is responsible for its propagation. It is often confined to one school, institution, or garrison, and it has been noticed that children sitting near one another in school are very liable to be infected. Fringuet in a school epidemic noticed that of thirty children seven were attacked, not all belonging to the same village, and of these, three of the boys and two of the girls had sat next to one another in school. Two or more cases often occur in the same house, a fact which has been noticed in almost every epidemic. Russell met with an instance of six cases in one house at Glasgow. Dr. Fowler tells me that in East Aberdeenshire he has often noticed two or more cases in one house, and in 1911 four out of five children in one instance took the disease. In former epidemics he has noticed that the first case is sometimes a child below school age and that the older children from 10 to 14 are affected later, and often in such cases no source of infection can be discovered. Falkner in an epidemic at Toowoomba in Australia showed that its propagation by personal contact was very evident and gave some striking instances, but also noticed cases scattered in the surrounding country where no contact could be proved. In camps and barracks the men occupying one room are liable to be affected, and often in a small outbreak only one part of the camp or one corridor of the barracks supplies the cases.

This has been noticed in the French and German armies. At St. Cloud forty-nine soldiers were affected, thirty-four in one battalion and fifteen others in the same battery of artillery, and of these ten were living in one room and nine in another. The infection seems able to linger in one place for some time.

Krasnobaeff records that three brothers were attacked at intervals of three to four weeks, and it was found that a child with jaundice had lived in the room in which they stayed for a few days. Schneekloth at Kiel met with three cases in one house: two sisters fell ill at eight days interval and an infant three months later. Other similar instances have been recorded. At Senlis seven cases of jaundice, one fatal, occurred in April 1885, and fourteen in the same barracks in February and March 1890, and two sporadic cases were noticed in 1889. It probably has considerable powers of resistance outside the body, but of this little is known, and it may also be able to live on the mucous membranes of individuals themselves immune, as happens in so many diseases, and this may explain the occurrence of isolated cases and those at the edge of an area where it is epidemic and where no contact with an affected person has been possible.

There has been considerable doubt as to how it gains entrance to the body, and indeed whether it is a general disease chiefly affecting the liver and hepatic ducts, or a local infection of the duodenum and lower end of the bile duct.

Meinert noticed that it was particularly liable to pick out individuals who were already suffering from respiratory disease due to antecedent influenza. It probably does gain entrance to the body through the naso-pharynx, and in Meinert's cases this in common with other parts of the respiratory tract was weakened and so gave ready ingress to the infecting agent. In 1912 Ralph Poignard described a small epidemic in Suffolk. There were ten cases in children between the age of 6 and 12, and slight pharyngitis was noticed in every case, this condition becoming better as the jaundice appeared. The gastro-intestinal symptoms appear to have been slight, though vomiting was noticed in three. In one instance, in which all the family slept in one room, only two became ill with jaundice.

In October 1911 I was unfortunate enough to fall a victim to the disease, and almost certainly contracted it from the servant who usually waits on me. Both of us had nasal catarrh, and I had some inflammation of the pharynx in addition, and I am convinced that this was no accident but an essential part of the illness. In 1910 three of my cousins were attacked by a severe form of the disease, and in one instance it apparently began with nasal catarrh, but this may have been an accidental complication. I have recently met with a case in a child which also began in this way. The following are the notes of these cases, though incomplete in many ways.

Cases.

Case I. Housemaid, aged 31. London. On October 5, 1911, she had sharp pains in the back and aching in all her limbs. There was no headache and no abdominal pain. Slight nasal catarrh was present and lasted two days, but no cough. The throat did not feel sore. The tongue was dry and furred, and there was some loss of appetite, which lasted for a week.

October 7 and 8. Vomited once each day. Slight constipation. Sharp pains in the shoulders and back, which occurred on and off for the next fortnight. Epigastric tenderness which lasted till October 30.

October 14. Bile pigment present in urine. No itching of the skin. Papular rose-coloured rash all over the face and chest. No sore throat. Temperature 99·6° F.

October 18. Rash still remains, and there is slight itching of the skin. Temperature 98·4° F.

October 19. The rash has spread on to arms and legs and does not itch.

October 21. Jaundice of conjunctiva and skin. Liver palpable just below costal margin, and tender. Spleen not palpable.

November 8. Jaundice very intense. The appetite is now ravenous.

November 12. The jaundice is disappearing and the liver is no longer palpable.

November 15. The pink papular erythema has appeared again.

December 1. Loss of appetite. Pain in right shoulder and across back. Sharp pain in epigastrium and tenderness over the liver, which is palpable. Jaundice deeper again and urine once more full of bile pigment. No albuminuria. Feels very depressed.

December 20. Deeply jaundiced. Stools whitish again. Feels better in general health.

January 4. Jaundice is gradually disappearing.

January 20. Still slightly jaundiced.

February 1. Jaundice of ocular conjunctiva is still just visible.

February 7. The jaundice had quite vanished.

The illness was notable for its commencement with nasal catarrh, the relapse with return of rash, loss of appetite and renewed swelling of the liver, and the long duration of the illness, 119 days, and persistence of the jaundice, 102 days.

No contact with any other case could be proved, but the cook had been in contact with a case in Aberdeenshire shortly before, and the caretaker of the house in which the illness began had been in contact with a case in London which had begun with fever and pains in the limbs.

Case II. This is a description of my own case. I was exposed to infection from the preceding case on October 5 and 6, and was then away from home until the evening of the 8th. I had been having most of my meals, except breakfast, away from home, and had had no water in the house at all.

October 9. Severe frontal headache. Stiffness and tenderness of the muscles at the nape of the neck, and aching and tenderness of the muscles of arms and legs. Slight nasal catarrh lasting two days, and cough due to pharyngeal inflammation lasting four to five days. Tonsils not swollen and follicles looked healthy. Slight shivering attacks. Temperature not taken. Tongue rather dry and furred. No nausea or vomiting. Loss of appetite. Urine very scanty.

October 10. Drowsy and irritable. Some epigastric discomfort and tenderness. The anorexia disappeared after four or five days, and returned with appearance of bile in the urine.

October 17. Itching of skin, but no jaundice. Urine very scanty and coffee-coloured, containing bile pigment. Some purpuric spots on right arm. Pain under right shoulder-blade and tenderness in region of liver.

October 21. Still very drowsy and irritable. Liver just palpable. Spleen not felt. Jaundice appeared in conjunctiva and skin, but was very slight at first and gradually deepened during next five days.

October 24. Stools quite white.

October 29. Deeply jaundiced. Aching pain under right shoulder-blade.

Small petechial haemorrhages on both arms above elbows. Feel better. Appetite returning. Lost 10 lb. in weight since beginning of attack.

November 8. Jaundice nearly disappeared. Aching under right shoulder at intervals.

November 15. No jaundice.

The infection was almost certainly air-borne, and the incubation period five days.

Case III. Boy aged $2\frac{11}{12}$ years. London.

December 6, 1911. Fretful. Nasal catarrh and slight cough, which lasted two to three days. Appetite poor. The mother thought it a slight cold. No pain in limbs. No diarrhoea and no constipation.

December 20. Urine very dark.

December 22. Jaundice of conjunctiva and face.

December 23. Jaundice universal. Stools very pale and offensive.

January 3. Liver one finger's breadth below costal margin. Spleen not felt. No albuminuria. Temperature 98·4° F.

January 24. Skin still jaundiced slightly. Appetite returned. No contact with another case of jaundice could be proved.

Cases IV, V, and *VI* occurred in one family in a brother and twin sisters in Sheffield.

Case IV.

September 22, 1910. The brother, aged $21\frac{8}{12}$ years, felt ill and shivered. Pain in back and limbs. Retching but no vomiting. Pain across abdomen. Temperature 103° F. Jaundice appeared a fortnight later, and constipation was very troublesome.

Case V.

October 18. His sister, $18\frac{6}{12}$ years, had severe pain across the back.

October 19. Temperature 105·4° F. Vomited and had severe pain in head, back, and left side of abdomen, with tenderness on pressure. Diarrhoea. Evening temperature 103° F. Jaundice began a week after the onset of illness.

Case VI.

October 28. Her twin sister had a slight cold with nasal catarrh, but did not feel ill.

November 1. Felt ill and remained in bed. Fainted when she tried to get up. Temperature normal.

November 2. In the evening the temperature suddenly rose to 105·8° F. Severe pain in head, back, and limbs, and in right epigastric region. There was no vomiting.

November 5. Jaundice with great irritation of skin, especially on the soles of the feet.

Sleeplessness was very troublesome.

Convalescence in all the cases was slow, and constipation was troublesome in the later stages.

Case VII.

Dr. Gale attended all the cases and kindly gave me details of them. He had only one meal in the house, on October 28, but was exposed to infection by inhalation on later days. On November 17 he was seized with malaise, temperature 101° to 102° F., and accompanied by gastro-intestinal symptoms, but

no jaundice developed. This may have been an abortive attack. As a child aged 7 or 8 he had a typical attack of epidemic catarrhal jaundice in company with three or four brothers and sisters.

If the first three were true catarrhal jaundice, as seems probable, the temperatures in two of the cases are higher than in any case of which I have seen a record.

The nasal catarrh in the one case may have been accidental, as it did not coincide with the onset of high temperature, but the illness evidently started at least one day before the temperature rose.

I can find no account of naso-pharyngeal inflammation in any published account of epidemic jaundice, but it may well have been overlooked, since one rarely has an opportunity of seeing a case until the jaundice is already present, and has probably distracted the attention of the patient from what he would regard as an unessential nasal or pharyngeal catarrh. There is no doubt that it is not present in the majority of cases, but it is probable that all are infected through this portal. The occurrence of tonsilitis has been occasionally noticed, but never in a series of cases, and no mention has been made of the stage of the disease at which it has appeared. In poliomyelitis, cerebrospinal meningitis, and some other diseases in which the organism almost certainly enters the body by this means, no inflammation is noticed in the great majority of instances.

The following case is also of interest from this point of view, though it was published as an example of malignant jaundice by Donkin in 1895:—

A child, aged 2 years, admitted to the hospital November 22: three weeks previously the illness began with a 'cold' and cough; no coryza. The appetite failed; constipation present. Was sleepy. Jaundice one week later. On admission the liver was felt one finger's breadth below the costal margin. The child was restless and got gradually worse. Petechiae appeared on the legs and the child vomited blood once. It was delirious, and later became comatose and died. No post mortem was allowed.

The illness began with pharyngeal inflammation, and might be regarded as a severe type of catarrhal jaundice or as acute yellow atrophy of the liver. As I shall show later, there is a good deal of evidence that the latter disease is merely a form of catarrhal jaundice occurring in individuals with some inherent weakness of the liver.

Discussion.

In epidemic catarrhal jaundice the incubation period is most commonly from four to ten days, but longer intervals have been observed. Dr. Fowler tells me that in his Aberdeenshire cases it has been under ten days as a rule. Guinon noticed an interval of nine days between the attacks of a brother and sister in the same house, and in my own case it was five days. Many of those with an incubation period apparently more than ten days and occurring in one house may be due to the fact that the patient who first started remained infectious for a few days and did not infect another case at the onset. Those following an interval of some weeks are probably due to virus remaining active in the rooms

occupied by the first patient. It is unknown how long an individual may remain infectious, but it is almost certain that the patient has practically ceased to be infectious when the jaundice has appeared. No case of infection has been recorded in a hospital ward.

Two main forms of the disease occur, though every gradation between them is met with. In the first there are no constitutional symptoms and often no pyrexia, and the first sign of illness noticed may be the jaundice. In the second there is a definite prodromal period with fever, which may last for from four to fourteen days before the appearance of jaundice. In some epidemics, especially the small ones, one of these forms may be present alone, as in those described by Cleghorn in Minorca; by Decaisne in Paris, in which twenty-eight cases occurred from October to December, all in adults; by Dalgleish in the summer and autumn of 1901 at Bloemfontein, in which adults only were attacked; by Rankin in Londonderry, in which eleven cases, all in children, were met with in July and August 1894; and by Bartlett, all in children, in all of which no prodrome and no pyrexia were met with.

In most epidemics both types are seen, as in that at Buxor Gaol in India, where a quarter of the cases were afebrile; in the extensive epidemic in the Kingdom of Saxony Meinert found there was no fever in 28 per cent. of the cases. In the South African War, on the other hand, all the cases were febrile.

In the afebrile cases there is usually merely jaundice, lasting on an average eleven days and accompanied at first by loss of appetite and constipation. The prodromal period in the febrile cases begins with malaise, headache, pain in the nape of the neck, back, and limbs, and the muscles may be tender. There is sometimes shivering and occasionally a rigor. Nausea, vomiting, loss of appetite, drowsiness, irritability, and sometimes sleeplessness, are present. The pulse is usually quickened, and the degree of pyrexia usually low, 100°–101° F., but temperatures of 103° and 104° F. have been noticed, and in two of the Sheffield cases the temperatures were 105·4° and 105·8° F. respectively. As in other infections, a high temperature does not always mean a correspondingly serious illness. The liver is always tender early in the disease, often painful, and generally if not invariably swollen. Jaundice appears as a rule between the fifth and fourteenth day, and with its appearance there may be a marked slowing of the pulse rate, which may fall to 40. The lessening of the pulse rate appears to be due in some cases to the action of bile salts on the cardiac ganglia, and in others to the influence of the central nervous system. The drowsiness and loss of appetite may increase at this period, but as a rule an improvement in general condition soon follows the appearance of jaundice. The spleen may be enlarged and may be easily palpable, but often there is no increase in size. The proportion of cases in which splenic enlargement occurs varies much in different epidemics. In some there is no enlargement; in others, as in the Pavia epidemic described by Martin, it was present in every case. There may be pain and tenderness over this organ. Dr. Fowler met with it in one child, and it was present in one of the Sheffield cases. Constipation is the rule, though occasionally

diarrhoea is present. The stools are pale in colour or quite white, according to the degree to which the bile duct is blocked, and later are often offensive. When the bile begins to flow again there may be slight meteorism and pain, but these disturbances are rare. Constipation is a common sequel to the disease, due perhaps to an alteration in the constituents of the bile; but of this there is no proof.

The condition of the urine varies. In some cases it is greatly diminished in quantity, 450 to 600 c.c. in twenty-four hours, even when the fever is low and there is no obvious sweating. Indeed, this last symptom is a rare one. The diminution in quantity and the presence of large amounts of bile pigment may be noticed before the jaundice. Urobilin and indican have also been found. When jaundice appears there may be a considerable increase in the urinary output, but there is not the marked polyuria which is met with in the urinary crisis of infectious jaundice.

Albumin is only present in a small proportion of cases. The function of the kidney cells seems to be interfered with more than structural changes would suggest. Valassapoulo and Widal and Abrami have noticed that this may occur in infectious jaundice, though in this there are often well-marked structural changes also.

The depth of the jaundice varies. Abortive cases probably occur in which it is entirely absent, but can only be recognized in epidemics, and seem to be very rare in these. One is given by Falkner in the Toowoomba epidemic, and the case I have already mentioned was also probably another example. Cases described as gastritis, for which no cause was found, occurred rather freely in the Bloemfontein epidemic and may have been of this nature. Elsewhere I find no mention of them. In the Aberdeenshire epidemic Dr. Fowler met with a case at the beginning of January 1912 in which, after a prodromal period of seven days, marked by drowsiness and persistent vomiting, jaundice appeared in the ocular conjunctiva, but there was no marked colouring of the skin and the jaundice had entirely disappeared three or four days later.

The jaundice, on the other hand, may be very protracted, as in the case already mentioned in which it lasted 102 days.

Relapse may occur after it has completely disappeared, and, though uncommon, cases in which they are met seem to be much more fatal than simple ones. Meinert describes one, in which there was initial fever, enlargement of the liver and spleen, and jaundice. The jaundice disappeared after two weeks, but there was a relapse a week later followed by cholaemia, with a temperature of 40° C. (104° F.), convulsions, coma, and death.

In the same epidemic, in a man aged 25 a relapse occurred eight weeks after recovery, in another aged 30 four weeks after recovery, and in a woman aged 40 it happened two weeks after the disappearance of a jaundice which had lasted four weeks. Griffin also records a relapse followed by death with every appearance of acute yellow atrophy, and others similar are mentioned in the literature.

The feeling of weakness and prostration is sometimes out of proportion to the severity of the symptoms, and convalescence, especially in adults, is often slow. There is a considerable loss of weight even in cases where the appetite is only lost for a short time. In a mild epidemic in France the average loss was 7 lb.

Deaths are very unusual; 161 occurred in a total of 22,569 cases amongst the Federal troops in America. Kissel in the Moscow epidemic found six out of ninety-six cases, in children aged $2\frac{5}{12}$, $3\frac{3}{12}$, $2\frac{6}{12}$, $1\frac{6}{12}$, $2\frac{6}{12}$, and 4 respectively. In the first four the liver was enlarged, and the spleen in the first two. There was albuminuria in the fourth. Microscopically the liver showed proliferation of the epithelium of the hepatic bile ducts and proliferation of the bile ducts themselves at the periphery of the liver lobules. The liver cells in the centre of the lobules were necrosed and all showed fatty degeneration. In the other two cases neither liver nor spleen were palpable. In all the fatal cases there were severe nervous symptoms, loss of consciousness, great restlessness, universal twitchings of muscles, and disturbances of respiration and the heart's action.

There were eight deaths in the Martinique epidemic of 1858, all in adults, and nine out of 313 cases in the epidemic in Saxony, aged $\frac{1}{3}$, $\frac{1}{2}$, 1, 4, 5, 11, 12, 60, and 68 years respectively. In one of these the symptoms and state of the liver resembled those seen in acute yellow atrophy. Of two deaths in the Parkhead epidemic, one in a woman of 36, the other in a child of $1\frac{2}{12}$, the former was recorded as acute yellow atrophy of the liver, but these will be discussed more fully later.

Ulrik states that in Denmark deaths are occasionally met with. In the epidemic at Buxor Gaol, of sixteen adults affected one case proved fatal. Of the deaths which occurred in these epidemics, excluding those in the American War, twelve were in children and twelve in adults, but owing to the different age incidence and different epidemics and the lack of complete statistics it is impossible to say at what age there is the greatest mortality.

An interesting point in connexion with epidemics of jaundice is their occasional association with outbreaks of enteric fever and influenza, both themselves capable of producing jaundice. Catarrhal jaundice and enteric fever were present together in the South African War, in the Bloemfontein, Rotherham, and King's Lynn epidemics, and in one in La Nouvelle, France. Enteric fever was met with in the Elbe epidemic and in the Zulu War epidemic, but the former was probably Weil's disease and the nature of the latter is doubtful. Jaundice complicating enteric fever is very rare, appearing in slightly over 1 per cent. of all cases, and there is no evidence that it has ever been sufficiently common to simulate any form of epidemic jaundice. Its chief importance is that it has led to the view that catarrhal jaundice is water-borne. The simultaneous presence of jaundice and influenza in the epidemic in Saxony was very striking, though the jaundice spread over a wider area than the influenza. It was so striking that Meinert considered the jaundice a sequel to influenza or a special form of this disease. Both diseases have occurred together in other epidemics, but in most it has been noticed that influenza has not been prevalent, and the association

seems to have been purely accidental. There is no bacteriological proof of their identity, except that of Bonome, who found the influenza bacillus in pure culture in the blood, liver, and spleen of two children with intestinal symptoms and jaundice, and the bacillus coli communis in the liver. Microscopically the liver showed a condition of acute yellow atrophy. In view of the fact that many other organisms have been found in fatal cases probably as terminal infections, this cannot be regarded as a proof that even those two were influenzal, much less that all others are. Brünler of Freiburg said that jaundice was so common in influenza that he used it for diagnosis, but in a further explanation stated that it was merely a slight yellow staining of the conjunctiva and not of the skin, and that there was no bile pigment in the urine. True obstructive jaundice following influenza has often been noticed in numerous epidemics, but only as a rare complication. Gastric influenza is usually accompanied by vomiting and diarrhoea, and not by the constipation which is so typical of catarrhal jaundice. Meinert's views have met with a very wide acceptance, but there seem to be no good grounds for regarding catarrhal jaundice as a form of influenza. It has been mentioned that many small and some widespread epidemics of this disease appear from time to time over a large part of the world, but nothing has been said of the permanent reservoir of the disease. This must be sought for in sporadic cases of the same character occurring in the same areas. These do occur quite commonly, and are known as cases of catarrhal jaundice, but are not regarded as examples of a specific infectious disease. Chauffard treated sporadic catarrhal jaundice and both forms of epidemic jaundice as the same disease, and thought some cases were perhaps contagious. Kelsch considered them due to a specific infection, but included Weil's disease with epidemic catarrhal jaundice, and owing to this considered it to be generated by ponds, mud, soil rich in vegetable and animal matter, and water holding such matter in suspension.

Rolleston thinks some cases of sporadic catarrhal jaundice are of the same nature as the epidemic form, but limits it to the febrile cases, and regards them as few in number.

There is no doubt that certain cases with gall-stone may have no pain and may closely simulate simple jaundice. New growths and ulcers in the neighbourhood of the ampulla of Vater may lead to inflammation, which may spread to the bile duct and lead to its occlusion. Even in the absence of such gross lesions gastro-intestinal inflammation may lead occasionally to the same condition. But it is remarkable how seldom jaundice is met with in individuals known to have gastric or duodenal ulcers or new growths, when the duct is not blocked by fibrous tissue or an extension of the growth itself. In the great majority of cases no cause for catarrhal jaundice can be found, and it is no more prone to occur in the subjects of a chronic gastritis or enteritis than in healthy children and young adults. Over-eating or rash indulgence in alcohol are considered to be the two commonest causes, as they have been since the days of Hippocrates, but the latter can be excluded in children, and in adults I have seldom been

able to trace the disease to any special indiscretion—not more often than might well be regarded as accidental.

If we consider it from the other point of view, regarding it as due to a specific infection, and compare it with the epidemic form, we find that it agrees with this very closely. So far as we know, the geographical range and the age and seasonal incidence are the same, and the symptoms and physical signs found in the two conditions show a close parallel. The prevalence of sporadic catarrhal jaundice varies much in different years, a fact we should not expect were it due to indiscretion in diet and a multitude of other causes, but which is a peculiarity of all infectious diseases. These yearly fluctuations were shown by Neumann in Berlin and by Kissel, and are demonstrated in the Reports of the Health of the Japanese Navy. Kissel stated that in one year there were sixteen cases out of a total of 10,292 patients and in another seventy-nine out of 24,328; and in the Japanese navy it fluctuates from 1·3 to 5·7 per 1,000. It has been agreed that the seasonal incidence in all countries is heavier in autumn, winter, and spring.

In the German army there are two to three cases per 1,000 men, sporadic and in small epidemics, and more than half the total cases fall in February, March, and April, and the greater number in these months is most noticeable in the sporadic examples. Neumann in Berlin found it commoner in the winter months. In France this is so obvious that there is a phrase in Paris, 'Il y a des mois où il pleut de la bile à Paris'. In England there is the same seasonal increase in autumn and winter, noticed by every one who has written on the subject and sufficiently great to be perceptible without collecting statistics.

The age of those chiefly affected by simple catarrhal jaundice is much the same as in the epidemic form: children and young adults are the chief sufferers, but infants and old people are not exempt.

Neumann's figures prove that children form nearly half the cases, and he gives a chart showing that the number of cases in children and adults has the same annual and seasonal variations. Neumann gives the following figures for the age incidence in round numbers: 42 per cent. in the first ten years of life, 11 per cent. between ten and twenty, 27 per cent. between twenty and thirty, 10 per cent. between thirty and forty, 6 per cent. between forty and fifty, 2 per cent. between fifty and sixty, and 2 per cent. between sixty and seventy.

Sée was one of the first to point out in epidemic jaundice how little the symptoms resemble ordinary gastro-enteritis, and considered its pathology different from that of simple catarrhal jaundice. But in this too they are much more like the prodromal symptoms of an infectious disease. The initial nausea and vomiting, the early constipation and loss of appetite, are such as characterize most specific fevers, and the later intestinal derangement may well be caused by the cutting off of such an important aid to digestion as the bile.

Two forms of the disease occur comparable to those in epidemics, one without prodrome and the other in which this is present. When there is no prodrome the jaundice may be the first thing noticed, or it may appear simultaneously with

loss of appetite or other signs of interference with the digestive functions. In the mild cases, apart from the jaundice nothing but constipation and slight loss of appetite may be noticed. Frerichs recorded gastro-intestinal symptoms in thirty-four out of forty-one cases, but Wickham Legg considers the proportion amongst his cases much lower.

It is noteworthy that children, in whom any gastro-intestinal disturbance quickly leads to vomiting and diarrhoea, frequently have less marked symptoms of this kind than adults. The prodromal symptoms when present are of the same character as in epidemics, but usually less marked, and malaise, headache, with dry, furred tongue, loss of appetite, constipation, nausea, or vomiting are most common, but diarrhoea is sometimes met with. Loss of appetite is almost invariable, but Bamberger describes a condition of abnormal increase of appetite, 'fames canina', and this existed in one of my cases of epidemic catarrhal jaundice, but it does not occur at the commencement of the illness. The proportion of apyretic cases is probably higher than in epidemics and the pyrexia when present is usually lower. Statistics are unreliable, owing to the fact that so many are not seen until the jaundice is established, and at this stage the temperature, if it had been raised a degree or two, would have fallen. It is probably raised much more frequently than is generally thought. Rolleston says that the temperature is seldom raised, Wickham Legg that it is not uncommon to meet with a temperature of 100° F. Hale White considers that the temperature is often raised and the pulse quickened in the prodrome and, if not, usually rises as jaundice appears. Still says that in simple catarrhal jaundice a slight rise of temperature is not uncommon in children. The pulse rate is often quickened, but may be much slowed in many instances owing to the presence of bile acids in the blood. The jaundice follows the onset of the illness usually between the fifth and fourteenth day, and the blocking of the duct may be complete or incomplete. It is usually more complete and lasting in catarrhal jaundice, sporadic or epidemic, than in any other epidemic disease with which it is commonly associated, such as yellow fever, relapsing fever, and Weil's disease or infectious jaundice. Very prolonged jaundice is occasionally met with, as in my epidemic case. Hélène Herzenstein has written a thesis on the subject, and describes cases lasting ninety-five to ninety-nine days. The jaundice varied in depth from time to time, and the increased jaundice corresponded to slight attacks of fever, which suggested that a secondary cholangitis may have occurred, but there was no permanent injury to the liver.

A case of Frerichs' lasting ninety-two days and one of Dieulafoy's lasting 155 are quoted by Chauffard. Still cites two cases in children lasting five and seven weeks respectively, and points out that the presence of gall-stones in these is most improbable owing to the great rarity of the condition in children.

Relapses also occur, the jaundice either deepening again or returning after it has entirely disappeared. Still mentions one instance in a child, whose jaundice lasted fourteen days and recurred again six weeks later. Second attacks are said to be not very unusual, and examples are given by Chauffard and Hennig,

the former of whom met with a case in which it occurred four times in five years. The liver is usually tender, sometimes painful, and frequently enlarged. The urine contains bile pigment, and very rarely albumin is also present. The same rashes are met with as in the epidemic form, urticaria being the commonest. Of the blood little is known. In catarrhal jaundice, whether sporadic or epidemic is not stated, Achard and Loeper find a special and constant condition. At the onset there is a very slight polymorphonuclear leucocytosis, followed by a rapid leucopenia, with relative increase of mononuclear cells so as to produce an inversion of the formula, and later in the disease a slight eosinophilia. If this is confirmed and found in both forms of the disease it may be of value in deciding their relationship. Most authors merely state that there is no leucocytosis.

Sporadic and epidemic catarrhal jaundice are found somewhat in the same way as sporadic and epidemic poliomyelitis, except that jaundice is more common in the sporadic form and met with more often and over a wider area in the epidemic form.

In both diseases fever and prodromal symptoms are very often absent in sporadic cases.

Little can be said of the pathology. In the few cases which have been examined death has been accidental or due to some other disease. A plug of mucus has been found in the entrance to the bile duct, or swelling of the mucous membrane of the bile duct, of the papilla of Vater and neighbouring part of the duodenum in some cases, and nothing abnormal in this region in others. Far too few cases have been examined for any certain conclusion to be drawn from these findings. The same difficulty is met with in mumps, which is often thought to be due to a spread of inflammation up the duct to the parotid gland. The entrance to Stenson's duct is seen to be swollen and the duct feels like a thickened cord, and saliva may be partially or completely prevented from escaping. When the testicle is involved a urethritis may occur, which is undoubtedly due to a spread down from the gland. The inflammation of Stenson's duct may also be a descending one.

There is strong evidence that mumps is a blood disease. The frequent occurrence of metastases in other and distant glands, and the occasional swelling in the testicle or pancreas without any involvement of the parotid gland or the involvement of the testis first, seem to prove that the infection reaches the parotid or other glands by the blood-stream. This is further supported by the existence of prodromal symptoms, of which pharyngitis is often the first, and which makes it probable that the pharynx is the place where the virus obtains entrance to the body. In catarrhal jaundice the liver is probably infected by the blood-stream and the infection may spread down the duct. The great rarity of gastro-intestinal trouble without jaundice in epidemics and the early appearance of tenderness over the liver also suggest that the liver is attacked primarily. Abortive cases occur in every form of infectious disease, and if the liver were attacked first we could readily understand that they would usually escape

notice; if the duodenum were the primary seat this would be less likely to occur. If the infection were an ascending one we should expect the pancreas to be involved more frequently than the liver, since the duct of Wirsung is much shorter than the ductus choledochus. We have ample proof that the small bile ducts and the liver itself are invaded in severe cases, but there is no evidence that the pancreas ever suffers. Palpable swelling of the gland, and glycosuria, the former of which is frequently and the latter occasionally met with in pancreatic mumps, do not occur, and diarrhoea, which is usually present when the pancreas is attacked in mumps, is strikingly absent in most cases of catarrhal jaundice. The discussion of catarrhal jaundice would be very incomplete without consideration of its relationship to acute yellow atrophy, using this word in its strict sense, a relationship which is probably very close.

The Relation to Acute Yellow Atrophy.

According to Wickham Legg the first reference to the disease was made by Ballonius in 1616, who mentions the case of a boy of noble birth, who became sullen and obstinate. He had jaundice and slight fever, and after fifteen days delirium arose, followed by convulsions and death. The liver was found to be ὑπόχλωρον. He gives some more doubtful early cases, and then reaches one in a child aged 5 years, mentioned by Morgagni in his *De sedibus*. In 1819 Martinet described a case in a boy aged 15, who died jaundiced and delirious, and in whom the liver was smaller than natural, almost pulpy and the colour of rhubarb, mixed with red streaks. Abercromby gives another in 1821, in a woman aged 50. Bright separated it as a distinct condition and recorded three cases in 1836, and in 1842 Rokitansky described and named it. It remains a very rare disease, but cases are described every year and from all parts of the world. Very diverse views as to its pathology and etiology have been expressed. It has been regarded as a degeneration or an inflammation of the liver, and the microscopical appearances would support either view. Buhl was the first to consider it a general disease. From the close resemblance between the symptoms and the pathological changes caused in man by phosphorus and in sheep by lupins or a fungus growing on them and those met with in idiopathic acute yellow atrophy, it has been thought that this is also caused by some poison carried from the alimentary canal, the formation of which is accounted for in many different ways. It is almost certain that some cases are associated with and probably directly due to the infection of syphilis, but the proportion is not a high one. In many of these there is some increase of fibrous tissue, often pericellular, which links them to cases of acute cirrhosis, and they should perhaps be classed with cases of icterus gravis rather than with acute yellow atrophy. The majority of the cases have nothing to do with this disease. A few have been described following various acute infective conditions, such as erysipelas, osteomyelitis, enteric fever, and diphtheria, and in some staphylococcus, streptococcus, pneumococcus, and bacillus coli have been found in the blood and liver. But in the great majority

of cases no organism has been found in the liver or blood, and its injection into animals has been harmless. It is probable that not all are due to any one condition, but even where staphylococcus and other organisms have been found they may have been a terminal infection and not primary.

The great majority of cases where no cause is found, and which begin like a simple catarrhal jaundice, are probably actual cases of this disease, as Frerichs, Schroder, and Davidson have believed. A few cases follow infectious jaundice or Weil's disease. Rolleston thinks that cases which recover—he collected twenty-eight, and others have been recorded more recently—may perhaps be classed as cases of epidemic catarrhal jaundice, but there seems to be no valid reason why fatal cases should not be included also. As I shall try to show, the geographical distribution, the seasonal and age incidence, symptoms, physical signs, and pathological findings agree with those of catarrhal jaundice, with certain exceptions for which special reasons are to be discovered. Further evidence is afforded by the presence of cases in epidemics or in houses where a case of simple catarrhal jaundice also occurred at the same time.

Some inorganic poisons or organic poisons of slight complexity are well known to produce the same effects as complex poisons elaborated by bacteria. Hunter has pointed out how closely the symptoms and pathological changes caused by toluylenediamin resemble those in the more rapidly fatal cases of infectious jaundice, and it seems not unreasonable to suppose that the poison produced by catarrhal jaundice may resemble phosphorus in its effects.

Cases have been described from most parts of Europe, including the British Isles, Norway, Russia, France, Germany, Italy, and Austria; from Asia, several have been recorded in India, and it has been met with in Java and Japan; from Egypt, West and South Africa; and from North America and Australia; and, as in epidemic catarrhal jaundice, no race seems to be exempt. Various European races, Negroes, Arabs, Hindus, and Pathans, are all liable to be affected. With regard to yearly fluctuations too few cases are recorded to give any useful information, but sometimes several cases are met with in rapid succession in one area. To ascertain the seasonal incidence, I have tabulated over 100 cases, excluding doubtful ones, where syphilis was present, and long cases, which may have been acute cirrhosis, and also cases occurring in epidemics of jaundice, and give Lebert's table for comparison.

	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
	10	17	5	8	9	3	4	8	8	6	14	14
Lebert—												
	9	10	6	2	9	7	7	6	7	9	8	7

Both show an increase in the winter months, but it is more striking in mine. The cases in my list are arranged according to the date of the onset, in Lebert's by the date of death. This arrangement was made because in some of his cases a definite date of onset could not be determined, and in others the illness was very long. This makes it probable that some cases of acute cirrhosis

are included, and no precautions were taken to exclude syphilitic cases. The slight rise which he found in the summer months may have been due to the inclusion of some cases following Weil's disease. The cases given in my list include as many English cases as possible to avoid this risk.

The earlier cases described were nearly all in young adults. Lebert only found one in eight between the ages of 10 and 15, and Thierfelder only twelve cases of children out of a total of 143, but more recently many have been recorded in children.

Wickham Legg found the following old cases recorded: one in a child of $3\frac{1}{2}$ years by Loeschner, 1856; two, a boy aged $4\frac{10}{12}$ and a girl aged $4\frac{6}{12}$, by Tuckwell, 1874; a boy aged $2\frac{1}{2}$ by Hilton Fagge, 1869; a boy aged $2\frac{1}{4}$ by Rehn, 1875; and a child aged $\frac{8}{12}$ by Senator, 1878. Merkel collected eighteen cases under 10 years of age and Schmidt sixteen, and Skormin has described six cases in infants. Of these only Merkel's are included in my table of ages. In thirty-one cases Frerichs found six between the ages of 10 and 20, twenty between the ages of 20 and 30, and three between 30 and 40. Phillips has recently collected forty-one cases in children, less than 10 per cent. of the total number of recorded cases.

Its great frequency in women is well known, and it occurs in the proportion of 2 women to 1 man in adult cases. This is due to its special incidence in pregnancy and to a less degree in the puerperium, shown by the fact that Legg found 25 pregnant out of 69 cases in women, Thierfelder 33 out of 88, and Frerichs 11 out of 22. Excluding cases in pregnancy the disease is commoner in men than women, as in simple catarrhal jaundice.

I have made the following table of age incidence, taking the same precautions as in compiling the one showing the seasonal incidence. Of 98 cases 30 occurred between birth and 9 years of age.

25	occurred	between	10 and 19	years of age
29 (12 pregnant)	„		20 and 29	„ „
9 (1 pregnant)	„		30 and 39	„ „
4	„		40 and 49	„ „
1	„		50 and 59	„ „

From this it will be seen that if the cases in pregnancy are eliminated, the majority of cases fall in childhood and adolescence. The age incidence is the same as that of catarrhal jaundice. The association of the disease with epidemic and sporadic catarrhal jaundice is very striking and sufficiently important to be given somewhat fully. No doubt further evidence could be collected from journals to which access is difficult.

1. West described two cases in children, both fatal. The disease was attributed to food poisoning, but on the most slender evidence. The children had been in contact.

2. Two cases were described in the *Lancet*, 1906, in young Arabs at Port Said. Both were fatal, and both occurred at the same time.

3. Zanardini, 1905, records a fatal case in a woman, and says epidemic jaundice was prevalent in the district at the time in May.

4. Creed and Scott Skirving reported two cases in 1888 in the *Australasian Medical Gazette* in pregnant women aged 24 and 23 respectively. Both recovered. One was ill in May, the other in July, and both lived near together.

5. Hayward, 1889, in the same journal describes a case in a pregnant woman aged 24, who died in coma. Ten days later her husband had prodromal symptoms of the same kind but more severe than those of his wife, and jaundice followed. He recovered, and the disease was attributed to alcoholic liquor, with which he had consoled himself after his wife's death.

6. Hardie, 1889–90, in the same journal mentions the case of a young lad who had catarrhal jaundice. The family feared infection, but were told there was no risk as the disease was not an infectious one. His sister, aged 28, in whose house he lived, and who was seven months pregnant, soon became jaundiced and a week later died of acute yellow atrophy. Hardie records four more cases in Brisbane in 1889, all in young pregnant women and all fatal. They lived in different parts of the town, and nothing is said as to the prevalence of catarrhal jaundice. It is remarkable how many Australian cases occurred in 1889 and 1890, and unfortunate that there is no record as to whether the number of cases of catarrhal jaundice was above the average or not.

7. Macdonald describes an epidemic in New South Wales in January. Sixty cases were met with, 56 in men working on a reservoir, 2 in women, and 2 in children. The women and children suffered most severely, and the women, aged 30 and 32 respectively, who were both pregnant, aborted but recovered. They both had the usual prodromal symptoms, and their temperature rose to 102° and 104° respectively. The jaundice lasted three weeks. Though not cases of acute yellow atrophy, they are interesting in that they show the greater severity of the disease in pregnancy.

8. Wentworth, 1906, records a case from Charlestown. In February a boy aged 5 and his sister had catarrhal jaundice. Both made apparent recovery, though the sister's was slow. In April the boy again had malaise and constipation, and again became jaundiced. The symptoms were slight, and he was walking out of doors within four days of death. The liver was not diminished in size, and the spleen was enlarged. Microscopically the liver showed the changes of acute yellow atrophy. Three-quarters of the liver cells were destroyed, and there was new bile duct proliferation, formation of fresh connective tissue, and infiltration by lymphoid cells. The smaller bile ducts were filled with greenish-yellow casts.

9. Meinert in the epidemic in Saxony (313 cases) states that one case of acute yellow atrophy of the liver occurred.

10. Meder reports a case in an epidemic attacking fifty soldiers. All the others were slight cases. There was no pyrexia. Macroscopical and microscopical investigation was made.

11. In an epidemic of catarrhal jaundice in Derbyshire, 1901, described by

Peck, there were sixty-nine cases. One ended in acute yellow atrophy, but the rest were of no great severity.

In the fatal case there was much destruction of liver cells, and the small bile ducts were blocked by overgrown epithelium. The kidneys showed fatty degeneration and cloudy swelling.

12. Bardinel describes an epidemic at Limoges, which was mild in every case except those in pregnant women. In them it was sometimes mild and benign, but in others was malign with abortion or premature delivery, ending in recovery or fatal 'ictère grave' with ataxia and coma, and the death of mother and child. The number of such cases is not given.

13. Ballot gives details of an epidemic in Martinique in 1858. Most of the cases were at St. Pierre. At the beginning of the year there were only mild catarrhal cases. By March they had become more febrile in character, even in the mild examples of the disease. In August cases diminished, but increased in number again in November and December. Severe cases were sometimes afebrile. There was headache and pain in the limbs, and the urine was very scanty. The liver was not enlarged, but there was epigastric tenderness. In a few cases epistaxis or haemorrhage from the bowel took place. There was no albuminuria. There was intestinal pain and slight meteorism when the bile began to flow again.

The most interesting point is that 8 pregnant women were attacked in St. Pierre, most of them five months pregnant; 7 of these aborted after fifteen days' jaundice, 2 children were born alive, and one, a seven months' baby, survived. The women had delirium, somnolence, and coma, and died three to thirty-eight hours after delivery. Two other pregnant women (5 months) in a neighbouring village were attacked but recovered, but a case in an unmarried woman of 60 ended in death, after a condition of great prostration leading to coma. No autopsy was obtained.

14. Russell, in the Parkhead epidemic in Glasgow in June and July, 1888, says a woman aged 36 died of acute yellow atrophy of the liver on July 8 after two months' illness, and on July 14 her child, aged $1\frac{2}{12}$ years, became ill and soon afterwards was seen to be jaundiced. The epidemic was almost confined to children.

15. Griffin, 1834, saw a woman aged 20 on the point of death. Two or three days before she had vomited and become jaundiced. She died comatose. Three weeks later her sister was seized with vomiting and jaundice, became comatose, and then gradually recovered after a relapse.

16. Two cases of Hanlon's are reported by Graves. In the first a girl of 17 was jaundiced, vomited altered blood, and died July 28, 1840. In March, 1841, her sister, aged 11, had a feverish cold, became jaundiced on the third day, and died on the fourth, after vomiting blood, in a convulsion. The liver was natural in size. In June, 1841, her sister, aged 8, fell ill with vomiting, jaundice, headache, and restlessness, but subsequently recovered.

These were at Portarlington in Ireland, and are remarkable for the length of interval between the different cases.

17. Dyce Duckworth and Wickham Legg reported two cases. A girl, aged 10, became jaundiced on May 2, 1870. On May 19 she was delirious, and died in coma on the 20th. The liver was natural in size, but microscopically showed great destruction of cells. There was also fatty degeneration of the kidneys. In February, 1872, her brother, aged 19, became jaundiced and delirious. He had been ill since October, 1870. After 'coffee-ground' vomiting he died. Microscopically the liver showed the changes usually seen in acute yellow atrophy.

As Ozanam showed, the cases may begin like a simple catarrhal jaundice with the usual prodromal symptoms, or the case may be fulminating and rapidly fatal, the jaundice being the earliest sign noticed. In most of the latter cases no doubt the disease has progressed unnoticed for some days and they correspond to the cases of catarrhal jaundice with no prodrome. They are often afebrile. In fact, a description of the mode of onset of acute yellow atrophy is identical with that of catarrhal jaundice. When prodromal symptoms are met with they are usually slight, as in most cases of simple catarrhal jaundice. The liver is tender and sometimes painful, and the spleen is enlarged in about a third of the cases. It has been noticed that in cases where death has been rapid the liver remains enlarged. Extreme atrophy usually occurs in the less rapid cases. In several instances the change has been watched from day to day, and the liver, enlarged at the beginning, has been observed to diminish rapidly in size and end in a loss of one-half or two-thirds of its substance, and to increase again if recovery takes place. These changes may be extremely rapid. In a case given in the St. Thomas's Hospital Reports, 1898, xxvii. 50, the liver of a woman, aged 28, was enlarged on December 28 and less than natural on January 1. In another described by Anning in a woman of 23, in the puerperium the liver was two inches above the costal edge on August 11 and on August 14 only one and a half inches of deep liver dullness remained. On August 15 it began to increase again and was natural in size on August 20, when the patient had recovered. This same wasting of the liver has been noticed in the less rapidly fatal cases of Weil's disease in Alexandria, in the others the liver remained enlarged. The same observation was made by Arnould and Coyne at Lille. The liver is probably enlarged in all cases of acute yellow atrophy in the early stages, though by the time symptoms of serious liver deficiency appear it may have become smaller than natural. Many rapidly fatal cases recently described, especially those in children, have shown a liver larger than natural at death, but on minute examination the changes characteristic of the disease have been found.

To make a fair comparison with catarrhal jaundice only the earlier signs and symptoms must be considered, and these show a close resemblance. The later symptoms can only be compared with those met in fatal catarrhal jaundice.

The condition of the pulse, usually somewhat quickened and occasionally slowed, is the same in both; the temperature may be raised a little or unaltered. The blood shows little or no leucocytosis, but I find no detailed account of its condition. Urticarial, erythematous, and roseolous rashes are met with, but

petechial haemorrhages under the skin are much more common in acute yellow atrophy, though it must be noted that they appear late, as do the other haemorrhages met with in this disease. They may occur from the stomach in the form of 'coffee-ground' vomit, from the intestine, and from the nose, but are seldom very copious. The severe nervous symptoms with which the disease terminates are very like those seen in fatal epidemic jaundice. Though their cause is unknown, they are met with in all conditions where the liver function is almost in abeyance. Albuminuria is fairly often present, but is only slight, and casts are generally absent. The urea is much diminished and the nitrogen excretion increased, but the quantity of urine is less than natural. In cases which recover a urinary crisis occurs, with great increase in quantity of urine and urea, both of which gradually sink till the normal level of output is reached. This exactly resembles the condition of affairs met with in many of the epidemic cases, and Chauffard considers that it almost certainly is present in simple sporadic cases, though actual proof is wanting.

The presence of leucin and tyrosin, which was formerly supposed to be pathognomonic, is no longer so regarded. One or both may be absent, and in any case only appear at the end of the illness. Tyrosin has been met with in epidemic jaundice. These substances probably come from the destroyed liver cells themselves, since crystals have been found in the liver substance in necrosed areas, and not from ordinary proteid metabolism, which the damaged liver has failed to complete in the usual way.

In comparing the pathological changes in the liver in fatal cases of epidemic catarrhal jaundice with those in acute yellow atrophy we find them variable, but the variation is parallel in both. The differences are only differences of degree. In epidemic jaundice Kissel found the bile duct epithelium proliferated; at the periphery of the liver lobules there was new growth of bile ducts and the liver cells showed fatty degeneration; at the centre of the lobules there was necrosis of liver cells. Hanot and others have found the same changes, fatty degeneration at the periphery and necrosis at the centre of the lobules, with new bile duct formation at the periphery. In Meder's case of acute yellow atrophy occurring in an epidemic the acini of liver in the yellow parts were diminished and the cells showed some fatty degeneration, in the red parts the acini were much diminished and there was extensive destruction of liver cells. Branching processes of newly proliferated bile ducts were found in the periphery of the lobules and in the interlobular connective tissue. In Peck's, which also occurred in an epidemic, there was much destruction of liver cells, and proliferation of the epithelium from the small bile ducts, not of the ducts themselves. In acute yellow atrophy Gabbi describes a lymphocytic infiltration in three isolated cases, and newly formed connective tissue which was most abundant in the most severely affected areas of liver.

Snell and Bunch have seen marked liver cell proliferation proved by the number of karyokinetic figures met with in their sections. Karyokinesis was observed by Widal and Abrami in a sporadic case of Weil's disease. Bauer

describes a case of acute yellow atrophy of the liver in a pregnant woman, in which recovery took place, but death resulted from acute miliary tuberculosis three months later. The liver showed marked evidences of regeneration. Others, such as Aby Bey Ibrahim, have observed appearances which suggest that liver cells are formed from the terminal cells of the newly formed bile ducts. MacCallum shows that probably both methods take place. In the areas where cell destruction is complete newly formed bile ducts penetrate and their terminal cells enlarge and function as liver cells, but where liver cells are left these proliferate and form fresh gland tissue. Regeneration of the liver has been observed both clinically and microscopically. Perhaps the rather slow recovery and the aching under the right shoulder experienced in some cases after an attack of epidemic jaundice may be explained by supposing that some destruction of liver substance followed by a process of regeneration has taken place.

The condition of the small bile ducts varies in both conditions. In some they appear to be natural, but probably contain thick bile; in others they are filled with epithelial débris. The changes in the kidneys are not always the same, and in both epidemic jaundice and acute yellow atrophy cloudy swelling or some degree of fatty degeneration of the parenchymatous elements has been found.

The fatal issue in epidemic catarrhal jaundice and in acute yellow atrophy does not seem to depend altogether on the intensity of the infection, but there seems to be in most cases another factor, the inherent weakness of the liver itself. Its frequency in pregnancy and the puerperium seems to confirm this. There is always a very great strain thrown on the liver at this time, and, as Miotti and others have shown, normal pregnancy results in fatty changes in the liver cells such as are seen in the less severely affected cells in acute yellow atrophy. Many fatal cases of the disease have been recorded in women who have already successfully passed through one or more pregnancies, which proves that some additional factor is needed. The additional strain, in my opinion, is thrown upon the liver by the specific organism of catarrhal jaundice, which acting on a liver already weakened results in a complete overthrow of its function. In children and non-pregnant adults who are affected, the liver may be abnormally weak either from some congenital or acquired cause, or the infection may be unusually severe.

In the former case we may compare the condition to that which sometimes follows chloroform anaesthesia, so-called delayed chloroform poisoning, and which may closely resemble acute yellow atrophy of the liver. This does not depend on the total amount of chloroform administered nor on its abnormal concentration in the blood for a short time, but rather on a special susceptibility of the liver cells to an amount of poison which produces trifling and temporary results in a normal individual. The connexion between the effect of the poison of epidemic jaundice and pregnancy is very well shown by the Limoges and Martinique epidemics, and to a less extent by Hardie, Hayward, and Macdonald's Australian cases. Probably in these the catarrhal jaundice or the pregnancy

alone would have produced no untoward result, together they generally proved fatal. Thus I regard catarrhal jaundice as a specific disease due to an unknown organism endemic over a wide area and appearing not uncommonly in restricted and very rarely in widespread epidemics. If the view of its pathology which I have suggested is correct, the name 'infective hepatitis' would more accurately express the condition than 'catarrhal jaundice'.

Acute yellow atrophy of the liver in nearly every instance I consider to be a sequel to this disease, and occurring in individuals in whom the liver at the time of the attack was already weakened and unable to bear the further strain caused by this infection.

Of all the specific infectious diseases catarrhal jaundice seems to be most closely allied to mumps, and indeed the two diseases are not very unlike. In both the infection probably takes place through the naso-pharynx, and both are probably blood infections. In mumps the parotid or other salivary glands are most frequently affected, but other glands, such as the testicles, ovaries, mammary glands, pancreas, thyroid or Bartholin's glands, may be affected. In jaundice the liver is the gland which suffers. In both diseases atrophy may occur; that of the testicle is not very uncommon in mumps, that of the liver is a rare occurrence in catarrhal jaundice. Both diseases may occur with or without a prodrome and may be afebrile in character, though less often in mumps than in catarrhal jaundice.

Mumps is infectious but requires rather close contact, and is very commonly confined to one school or part of a school or to one part of a garrison. In one case, for example, twenty-three soldiers were attacked in one wing of a castle and none in the other, four room-mates being the first to contract the disease.

The infectiousness seems to vary much in different countries or in the same countries at different times, and it was long before its infectious nature was recognized. The infection may linger in a virulent condition in a room for a considerable time, as happens in catarrhal jaundice. The disease is undoubtedly air-borne, the organisms probably being spread in talking. Except that the infectivity of jaundice is, as a rule, considerably less, it seems to resemble that of mumps very closely indeed. The mortality in both is very low.

Summary.

1. Most epidemics of jaundice, in which the possibility of yellow fever, relapsing fever, and malaria have been excluded, are due to infectious jaundice or epidemic catarrhal jaundice.

2. Infectious jaundice or Weil's disease is in all probability due to the ingestion of contaminated water or food, but may be due to some biting insect.

Epidemic catarrhal jaundice is air-borne.

3. Epidemic catarrhal jaundice is much the commoner disease and is of almost world-wide distribution; infectious jaundice is met with chiefly round the Mediterranean Sea, and does not extend to the British Isles.

4. Simple catarrhal jaundice, usually attributed to gastro-duodenal catarrh, of varying origin, is the sporadic or endemic form of epidemic catarrhal jaundice, except in a comparatively small number of cases.

5. Acute yellow atrophy of the liver in the great majority of instances is due to the same organism acting on a liver weakened by some temporary strain, such as pregnancy, or having some inherent weakness. A similar condition may be produced by syphilis, infectious jaundice, and other infections, but much less often.

6. Sporadic and epidemic catarrhal jaundice and acute yellow atrophy of the liver are due in the great majority of cases to the same cause, a specific organism of unknown nature.

REFERENCES.

Abercrombie, *Path. and Practical Researches on Diseases of the Stomach*, Edinb., 1828.
Achard et Loeper, *Compt. Rend. Soc. de Biol.*, Paris, 1901, liii. 218.
Anderson, *Brit. Med. Journ.*, 1904, ii. 673.
Anning, *Lancet*, Lond., 1906, ii. 936.
Arnott, *Trans. of Bombay Med. Soc.*, 1st ser., x. 28.
Arnould et Coyne, *Gaz. Méd. de Paris*, 1877.
Ashby, *Brit. Med. Journ.*, 1882, ii. 947.
Ballonius (quoted by Bonetus), *Sepulchretum Generae*, 1700, Lib. iii, Sect. xviii, ob. 6.
Ballot, *Gazette des hôpitaux*, 1859, No. 62.
Bamberger, *Krankheiten des chylopoëtischen Systems*, 1855.
Banti, *Deutsch. med. Wochenschr.*, 1895, 493.
Bardinel, *Gaz. Méd. de Paris*, 1863, xlv. 732.
Barker, *Assoc. Med. Journ.*, 1854, Jan., 80.
Barker and Sladen, *Johns Hopkins Hosp. Bull.*, Balt., 1909, xx. 310.
Barthez and Rilliet, *Handbuch der Kinderkrankheiten*, Leipzig, 1855, ii. 32.
Bartlett and Pope, *Brit. Med. Journ.*, 1894, i. 407.
Batt, *Memor. della Società Med. di Emulazione di Genova*, 1801, i. 63.
Bauer, *Verhandlungen des Congresses f. Innere Medicin*, 1893, 185.
Bonome, *Lo Sperimentale*, 1903, lvii. 736.
Bright, *Guy's Hosp. Reports*, 1836, i. 621.
Brooks, H., *Arch. of Neurology and Psychopathy*, liii. 343.
Brunton, Lauder, and Tunnicliffe, F. W., *St. Bartholomew's Hosp. Rep.*, 1896, xxxii. 425.
Bugbee, *Med. Progress*, Louisville, 1908, xxiv. 367.
Buhl, *Zeitschrift f. rat. Med.*, Heidelb., 1854, iv. 355.
Calvert, *Brit. Med. Journ.*, 1894, i. 239.
Carville, *Arch. Gén. de Méd.*, Paris, 1864, No. 1, Ser. iv, 130 and 310.
Cavafy, *Lancet*, Lond., 1897, ii. 145.
Champneys, *Brit. Med. Journ.*, 1888, ii. 521.
Chauffard, *Charcot's Traité de Méd.*, v. 92.
Cleghorn, *Ep. Diseases of Minorca*, 1744–9.
Costa, S., *Rev. de Méd.*, Paris, 1904, xxiv. 89.
Creed and Scott Skirving, *Australasian Med. Gaz.*, 1888, viii. 259.
Cullen, *Brit. Med. Journ.*, 1894, i. 828.
Dalgleish, *Lancet*, Lond., 1901, ii. 523.
Descaisne, *Med. Times and Gazette*, Lond., 1872, i. 138.
Dieulafoy, *Semaine médicale*, Paris, 1888, 270.
Dixon, *Trans. Med. Assoc. Alabama*, 1908, 432 ; *Alabama Med. Journ.*, 1907–8, xx. 320–4.
Dominici, *Schneekloth, Thèse de Kiel*, 1900.
Donkin, *Lancet*, Lond., 1895, i. 28.
Dyce Duckworth and Wickham Legg, *St. Bart.'s Hosp. Rep.*, 1871, vii. 208.
Eppinger, *Wiener klin. Wochenschr.*, 1908, xxi. 480.
Esler, *Australasian Med. Gaz.*, 1902, xxi. 523.
Fagge, Hilton, *Trans. Path. Soc.*, Lond., 1869, xx. 212.
Falkner, *Australasian Med. Gazette*, 1902, xxi. 256.
Frerichs, *Klinik der Leber-Krankheiten.*
Fringuet, *Presse Médicale*, 1899, No. 53.
Gabbi, *Lo Sperimentale*, 1892, 232.
Girode, *Arch. gén. de Méd.*, Paris, 1891, i. 26.
Griffin, *Lond. Med. Gaz.*, 1834, xiii. 801.

Guinon, *Bull. de la Soc. Méd. des hôpitaux*, 1910, xxx. 685, 3rd series.
Hagenbeck, *Korrespondenzblatt f. Schweizer Ärtze v. Jahry. 1875*, xix. 545.
Hanlon (quoted by Graves), *Clin. Lect.*, Dublin, 1864, 634.
Hanot, *Semaine médicale*, Paris, 1893, 229 and 349.
Hardie, *Australasian Med. Gazette*, 1889–90, ix. 179.
Hawthorn, *Brit. Med. Journ.*, 1894, i. 523.
Hayward, *Australasian Med. Gazette*, 1889–90, ix. 288.
Henoch, *Vorlesungen über Kinderkrankheiten*, Berlin, 1881, 501.
Herzenstein, *Thèse de Paris*, 1890.
Hirsch, *Handb. of Geographical and Historical Pathology*, Lond. (New Syd. Soc.), 1886, iii. 287.
Holmes, *Brit. Med. Journ.*, 1894, i. 681.
Hunter, *Allbutt's System of Medicine*, Lond., iv.
Jaeger, *Zeitschr. f. Hygiene*, Leipz., xii. 525.
Jehn, *Deutsch. med. Wochenschr.*, 1885, 339 and 354.
Kelsch, *Traité de Mal. Épidém.*, 179; and *Rev. de Méd.*, Paris, 1886, vi. 657.
Kercksig, *Hufeland's Journal der Heilkunde*, 1799, vii. 3. 94.
Kershaw, *Brit. Med. Journ.*, 1901, ii. 1660.
Kissel, A. A., *Jahrb. f. Kinderheilkunde*, 1898, xlviii. 235.
v. Kolli, *Wratschch. Sapisk.*, 1896, Nos. 6 and 7.
Krassnobaeff, *Detskaja Medicina*, 1896, No. 2, p. 90.
Lamphear (quoted by H. D. Rolleston), *Diseases of the Liver*, 1905.
Landouzy, *Gaz. des hôpitaux*, Paris, 1883, lvi. 809.
Lanz, *Wien. klin. Wochenschr.*, 1894, 86.
Legg, Wickham, *On the Bile, Jaundice, and Bilious Diseases*, 1880.
Lebert (quoted by Wickham Legg), *Ibid.*
Libman, *Philad. Med. Journ.*, 1899, 620.
Lurman, *Berlin. klin. Wochenschr.*, 1885, No. 2.
MacCallum, *Johns Hopkins Hosp. Rep.*, 1902, x. 375.
MacDonald, *Australasian Med. Gazette*, 1886–8, vi, vii, 7. 247.
Marchand, *Ziegler's Beiträge zur path. Anat. u. z. allg. Path.*, Jena, 1895, xvii. 206.
Martin, *Rec. Mém. de Méd. mil.*, 1878, iii. 374.
Martinet, *Bibliotheca Med.*, 1819, lxvi. 350.
Mathias, *Brit. Med. Journ.*, 1904, ii. 675.
Mathieu, *Rev. de Méd.*, Paris, 1886, vi. 633.
Meder, *Ziegler's Beiträge z. path. Anat. u. z. allg. Path.*, Jena, 1895, xvii. 143.
Meinert, *Jahresbericht der Gesellschaft für Natur- und Heilkunde in Dresden*, 1889–90, 129.
Mende, *Hufeland's Journal der Heilkunde*, 1810.
Merkel, *Münch. med. Wochenschr.*, 1894, 89.
Miotti, *Annali di Obstet. e Ginecologia*, 1900, xxii. 733.
Moore, *Twentieth Century Medicine* (Article on Influenza).
Neumann, *Deutsch. med. Wochenschr.*, 1899, xxv. 574.
Ord (quoted by Mathias), *Brit. Med. Journ.*, 1904, ii. 675.
Orme, *Brit. Med. Journ.*, 1908, i. 499.
Peck, *Brit. Med. Journ.*, 1901, ii. 1659.
Pfuhl, *Berl. klin. Wochenschr.*, 1891, xxviii. 1178.
Phillips, *Amer. Journ. of Med. Sci.*, 1912, cxliii. 177.
Pinniger, *Brit. Med. Journ.*, 1911, ii. 1353.
Pissas, *Congrès des Médecins grecs à Athènes*, Constant., 1803, 18.
Plowright, *Brit. Med. Journ.*, 1896, i. 1321.
Podwyssoski, *Ziegler's Beiträge zur path. Anat. u. z. allg. Path.*, Jena, 1886, 259.
Poignand, *Brit. Med. Journ.*, 1912, i. 72.
Ponfick, *Virch. Arch. f. path. Anat. u. Physiol.*, Berlin, 1895, cxxxviii, Suppl. 81.
Quincke (quoted by Chauffard), *Charcot's Traité de Méd.*, v. 92.
Rankin, *Brit. Med. Journ.*, 1894, i. 1122.
Raymond, *Med. Age*, Detroit, Oct. 10, 1892.
Rehn, *Jahrb. für Kinderheilkunde*, 1870, iii. 197; *Berl. klin. Wochenschr.*, 1875, 649.
Renon, *Granchet's Traité des Maladies de l'Enfance*, iii. 163.
Révillout, *Gaz. des hôpitaux*, Paris, 1871, 573.
Rizet, *Rec. Mém. de Méd. militaire*, 1867.
Roche, *Brit. Med. Journ.*, 1894, i. 523.
Rokitansky, *Handb. der path. Anat.*, Wien, 1842, iii. 313.
Rolleston, H. D., *Diseases of the Liver*, 1905, 584; *Encyclopaedia Medica.*
Rouffignac, *Thèse de Paris*, 1885.
Rufz, *Philad. Med. Trans.*
Russell, *Brit. Med. Journ.*, 1888, ii. 326.
Sandwith, *Brit. Med. Journ.*, 1904, ii. 672; *Medical Diseases of Egypt*, Part I, 1905.
Sato, *Kyo-rin-no Shiori*, Tokio, 1901, xiii. 461.
Satterlee, *Med. News*, N. Y., 1903, 1069.

Schmidt, *Dissertation*, Kiel, 1897.
Sée, *Gaz. des hôpitaux*, 1872, Paris, 201.
Semmola and Geoffredi, *Twentieth Century Medicine* (Article on Jaundice).
Snell and Bunch, *Lancet*, Lond., 1895, ii. 459.
Still, *Clin. Journ.*, 1900–1901, 321.
Sver, *Sundhet's-Collegii Berättelse år* 1858, 74; 1859, 79.
Thierfelder, *Handbuch der speciellen Path. und Therapie*, 1880, viii. 267.
Thursfield, *Brit. Med. Journ.*, 1894, i. 522.
Toelg and Neusser, *Zeitschr. f. klin. Med.*, Berlin, 1884, vii. 321.
Tuckwell, *St. Bartholomew's Hospital Rep.*, Lond., 1874, x. 39.
Tymowski (quoted by Chauffard), *Charcot's Traité de Méd.*, v. 99.
Ulrik and Fringuet, *Schneekloth, Thèse de Kiel*, 1900.
Vaisey, *Brit. Med. Journ.*, 1911, i. 935.
Valassapoulo, *Bull. et Mém. de la Soc. méd. des hôp. de Paris*, 1908, sér. iii, xxv. 753.
Vetlesen, *Norsk Mag. f. Lægevidensk.*, Christiania, 1887, iv. ii. 380.
Viguier, *Arch. de Médecine et Pharm. militaire*, 1904, xliv. 25.
Weil, *Deutsch. Arch. f. klin. Med.*, Leipz., 1886, xxxix. 209.
Wentworth, *Arch. Pediatrics*, 1906, xxiii. 81.
West, *Trans. Path. Soc.*, Lond., 1880, xxxi. 116.
Widal and Abrami, *Bull. Soc. méd. des hôpitaux*, 1908, 524.
Woolfryes (Zulu War), *Army Med. Dept. Reports*, 1879, Appendix iv. 305.
Worm, *Rec. Mém. de Méd. mil.*, 1865.
Worms, *Gaz. hebd. de Méd.*, 1865, xxxiii. 518.
Young, *Brit. Med. Journ.*, 1894, i. 463.
Zanardini, *Gazz. d. osp.*, Milano, 1905, xxv. 361.

Since this paper was written I have met with another case of catarrhal jaundice with pharyngeal symptoms. The patient, a surgeon, kindly gave me the following details of his illness, which began at the end of August, 1912.

Prodromal symptoms. General malaise. Slightly raised temperature.

No loss of appetite.

Slight catarrh of the lower part of pharynx, causing an irritating cough, but no sputum and lasting four days. No nasal catarrh. No pains in limbs.

Fifth day: loss of appetite and severe nausea. No vomiting. Felt chilly: no rigor. This condition lasted four days.

On the ninth day of the illness bile pigment was present in the urine and the urine became scanty.

On the tenth day there was slight jaundice of the conjunctiva and later in the day of the skin. There was no obvious enlargement of the liver, but a feeling of discomfort in the hepatic region.

Constipation was present throughout the illness.

The jaundice lasted about a week.

THE ACTION OF DIASTASE IN DIABETES MELLITUS

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Diabetes Mellitus.

The fertile but complex field which experimental medicine has opened up in the study of glycosuria in animals directs attention to facts which may be of profound importance in clinical medicine. Diabetes is a disease which the knowledge of the past few years shows may have many possible factors, and a rational conception of the disease must be based on the recognition of the possibility of there being one or more of these factors present in each case. Further inquiry is necessary to determine what relation there is between the findings in animals that the nervous system, the ductless glands, the pancreas, and the liver are correlated for carbohydrate metabolism, and the disorders of that metabolism as shown by diabetes in man. While there can be no doubt that disturbances of the central and sympathetic nervous system, of the liver, pancreas, adrenals, thyroid, and alimentary system may cause glycosuria in animals, there is yet little evidence to show how and when any of these are connected with diabetes mellitus in man. Many efforts have been made to treat the disease by therapeutic measures based on these findings, but, so far, ductless gland therapy has yielded little if any result.

The question arises, to what point in these possible cycles of events new methods of treatment are to be directed. So far no drug has been found which exerts a specific effect on the disease, and treatment is almost entirely confined to dietetics. Progress which can so far be noted has been made on these lines, and in the past few years increased knowledge of the chemistry and physiology of food-stuffs has forwarded this progress considerably. Whichever of the above-mentioned factors may be the cause in any particular case of diabetes, it is now recognized that a great deal of individualization is necessary in treatment.

In all the methods of treatment hitherto adopted none are more remarkable in the results sometimes obtained than the 'Oatmeal Cure' advocated by von Noorden. The work of certain French authors has shown that similar results are occasionally to be obtained with potatoes. Duhring has recorded that sometimes rice may be tolerated and not other carbohydrates. These results undoubtedly show the importance of the individual factor in each case.

[Q. J. M., Oct., 1912.]

It may be asked whether in these striking occurrences there is not some body (maybe differing in each case) which brings about the utilization of the starch. If there be such a body, the following work tends to show that it is not a diastase ferment. There is one final common factor which occurs in all cases, and that is the inability of the cells to utilize the sugar brought to them by the blood. Apart from a few rare cases there is a common hyperglycaemia. If any means be found to bring about the utilization of this sugar by the cells, then whatever the underlying factor, whether in alimentary, nervous, or ductless gland systems, progress in treatment could be recorded. Clinical experience shows that if in the diabetic the urine be rendered sugar free, then life is prolonged and complications are not likely to arise.

From the point of view of treatment three conceptions of this hyperglycaemia may be considered: (1) The products of glycogenolysis may be yielded to the blood, not in the form of biological glucose, but in some other form which the cells cannot utilize. (2) The glucose produced may be normal but the cells incapable of using it. (3) The primary splitting up of the glucose molecule to lower bodies which the cell can use may be inhibited. If the glucose, whether biological or otherwise, could be split up by some substance introduced into the blood from without, it is probable that the cells would be able to make use of the lower bodies so produced, and the consequent errors of protein and fat metabolism would be averted.

It is generally recognized that the formation of glycogen from glucose, the reversed reaction, the formation of fat from glucose, and the combustion of glucose are all diminished in the disease. In the combustion of glucose the difficulty lies in the first stage, before the formation of lactic acid. So far, while there have been many attempts to explain this difficulty, the most likely explanation is that the deficiency is in the zymo-excitor of the ferment as suggested by Cohnheim. There is some reason to consider it possible to supply a body which can assist in the combustion of glucose in true diabetes. As stated above, the diabetic may show a peculiar tolerance for starch administered in certain forms. An example of this in the case of oatmeal is strikingly shown in Chart I. It is possible that when such a result is obtained it may be due to the presence of some substance in the oatmeal which aids the combustion of glucose.

The following work is the first part of an attempt to determine if such a substance is to be found in oatmeal. It is obvious that in any search for such a body the first to be considered are the carbohydrate-splitting ferments, the diastases. Diastase has been used in the treatment of disease, but the recorded results are at variance. Beardsley (1) considered that the administration of takadiastase to a diabetic has a tendency to alleviate all the symptoms. Wakeman (2) is of opinion that diastase is of no value, that it increases the somatic acidity and is thus harmful in its effects. In the cases recorded below we have attempted carefully to examine from every point of view the influence of diastase upon the progress of the disease.

As a result of the study of the cases it will be seen that, apart from some slight action on the reactivity of the urine, little effect can be observed on metabolism. In one case, J. H., female, aged 19 years, it appeared possible at first that the drug may have had a beneficial action, but the patient subsequent to

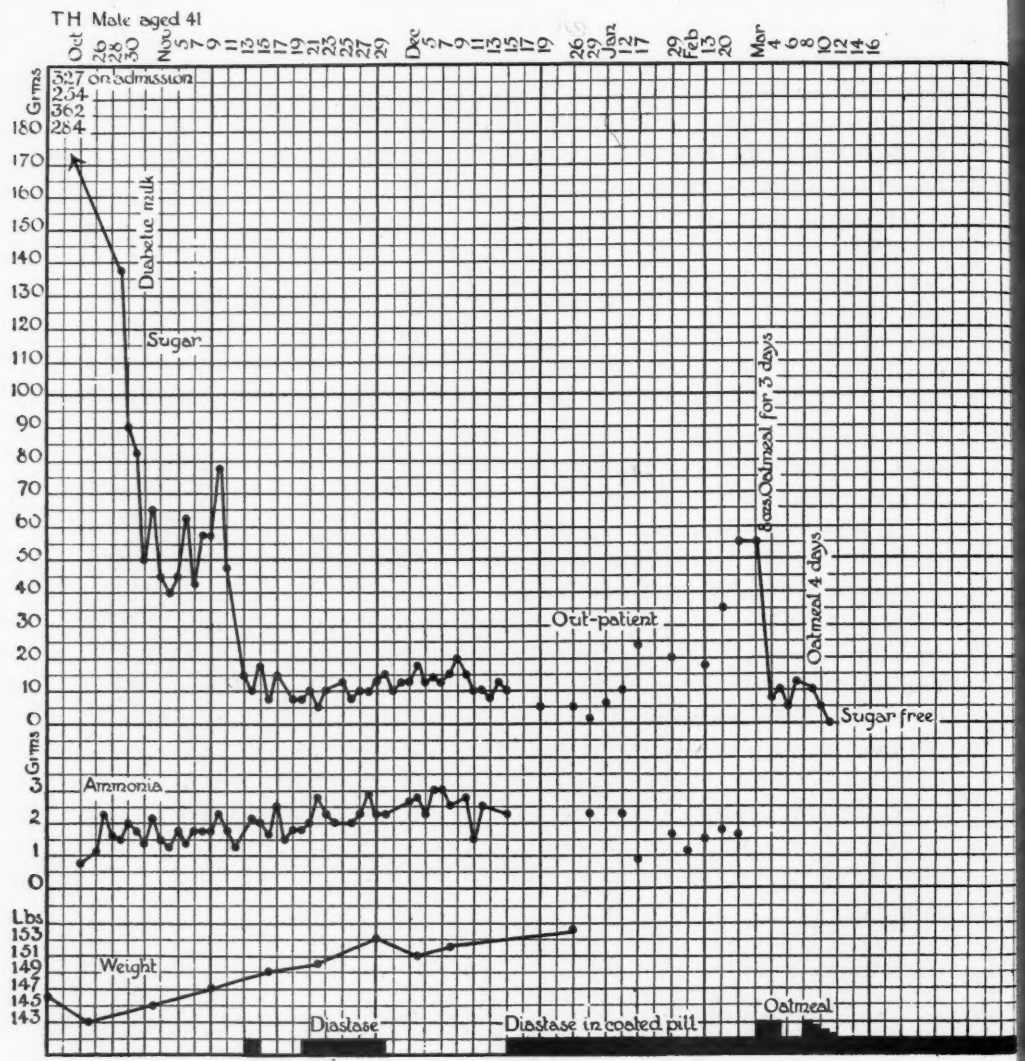


CHART I.

leaving hospital has again relapsed, though still on diastase, and no definite progress can be recorded apart from that obtained by diet.

Before the administration of diastase to a diabetic we have in each case estimated the diastatic power of the patient's saliva, and the results show there

is little, if any, diminution in diabetic as compared with normal saliva. Using Roberts's method, we found that saliva from a series of normal individuals gave an average diastatic value of 20, whereas from a series of diabetics the value varied from 7 to 33, the low values being found at one time of the day, but in every case at certain periods of the day a normal average could be obtained, except in one case. The diastatic power of the saliva and of the preparations we used in treatment were all inhibited and destroyed by a 0·2 per cent. solution of hydrochloric acid. Therefore, in some of the cases diastase was given in coated capsules or in coated pill in an endeavour to get the diastase absorbed unaltered from the small intestine. Dr. Thurston Holland kindly tested these for us and demonstrated that the capsules when enclosing bismuth carbonate withstood the action of the stomach juice for periods up to six hours.

In some cases the action of takadiastase (not in capsules) was investigated, as the beneficial effects recorded by Beardsley were obtained with this preparation. The diastase in solution which was for a time given in two of the cases was obtained from malt by precipitation with alcohol. In one of these cases alteration in the reactivity of the urine was found with this liquid preparation, when the diastase ferment was obviously killed in the stomach. It is most probable that in all the other cases, as in this, the altered reactivity of the urine was due to something present in the diastase preparation and not to the ferment itself.

In all the cases the sugar was estimated daily for long periods, as shown in the charts. The estimations were made by Pavy and Gerhardt's methods, periodically controlled gravimetrically. In two of the cases the food was accurately weighed each day for a month, and the nitrogen and fat content calculated. The nitrogen excreted in the urine and stools was determined by the Kjeldahl method. The acetone and diacetic acid were examined qualitatively daily. The ammonia excretion was estimated by Schlössing's method, except in the later cases, when the quicker method of Mathieson was used.

Case I. T. H., male, aged 41 years, was admitted to the Royal Infirmary, Liverpool, on Oct. 18, 1911, under the care of Dr. Abram, suffering from great thirst, headache, and loss of weight. He had frequent micturition, rising as often as every half-hour at night. Six months prior to admission he had a feeling as of 'pins and needles' in the hands. The thirst commenced in September, 1911.

Nothing of import was elicited in either the family or past history. On admission he weighed 10 stone 7 lb. He was fairly well nourished. The circulatory, respiratory, alimentary, and nervous systems were normal. The urine was passed in quantities up to 148 ounces and contained as much as 360 grammes of sugar daily. With a gradual restriction of carbohydrate diet the sugar was brought to an average of 60 grammes per day.

On Nov. 1 the patient was allowed 1 litre of sugar-free (diabetic) milk daily. The sugar continued to be excreted in about the same amount until Nov. 12. Two days later the sugar had come down to an average of about 10 grammes daily. It kept at this or a slightly higher level until his discharge on Nov. 18. During this period he was on strict diabetic diet.

From Oct. 22 until Dec. 16 a careful study of nitrogen and fat metabolism

was made. As will be seen from Chart II, the nitrogen intake up to the period when he was put on diabetic milk was between 30 and 40 grammes per day, and there was very little nitrogen gain. On Nov. 13 he was put on 0·3 gramme of Merck's absolute diastase in capsules for two days, and again on Nov. 23 for seven days. As will be seen from Chart II, during the second period there was

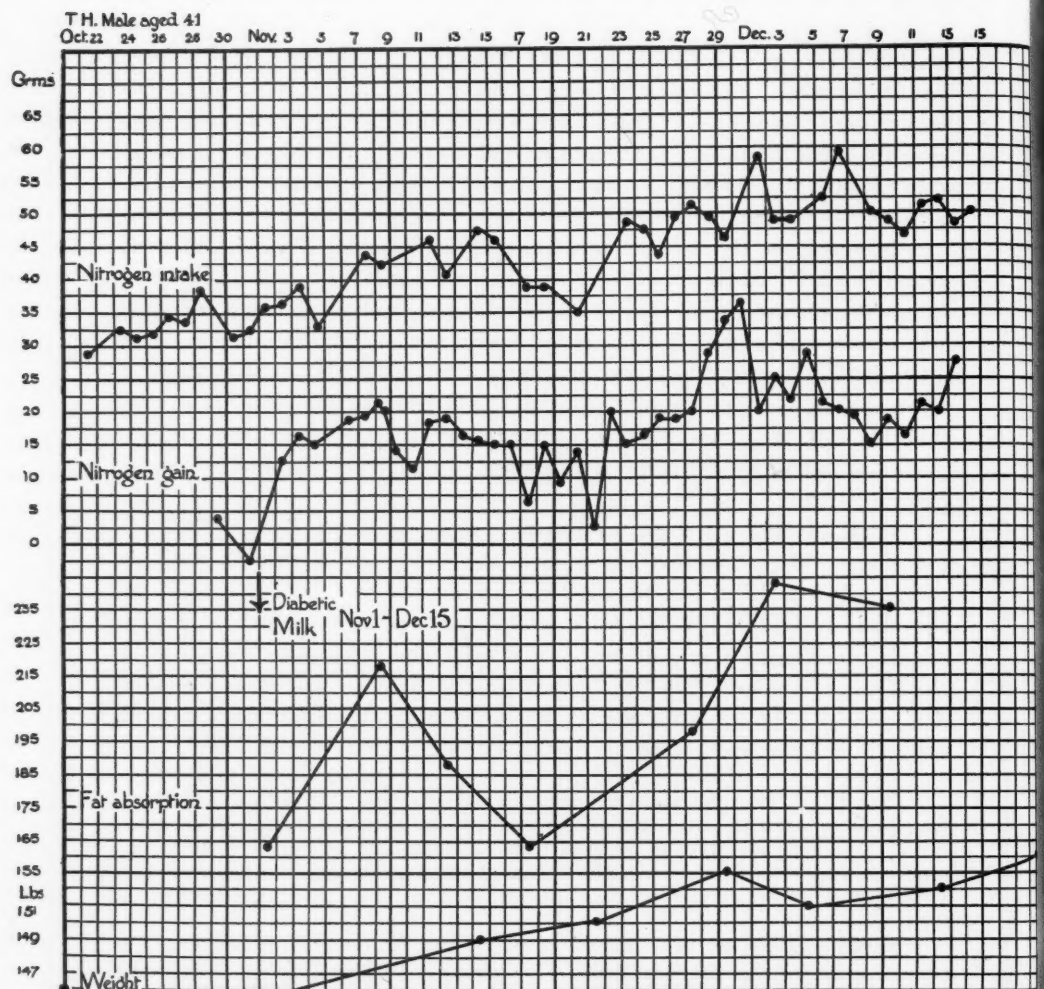


CHART II.

a slight rise in nitrogen intake and in nitrogen gain, and a great rise in fat absorption. The effect on fat absorption in this case might be due to the diastase, but in other cases we have found no effect whatever. In Case IV the withdrawal of takadiastase, on which the patient had been for six weeks, made no difference whatever to the fat absorption.

On Oct. 15 he left hospital, and from this date the diastase was continued three times daily. The sugar excretion gradually rose, and on March 1 the sugar output was 56 grammes per day. The patient was feeling weak and complaining of thirst. He was readmitted, and for two days was fed on green vegetables with 8 ounces of butter and two eggs daily; for the next three days

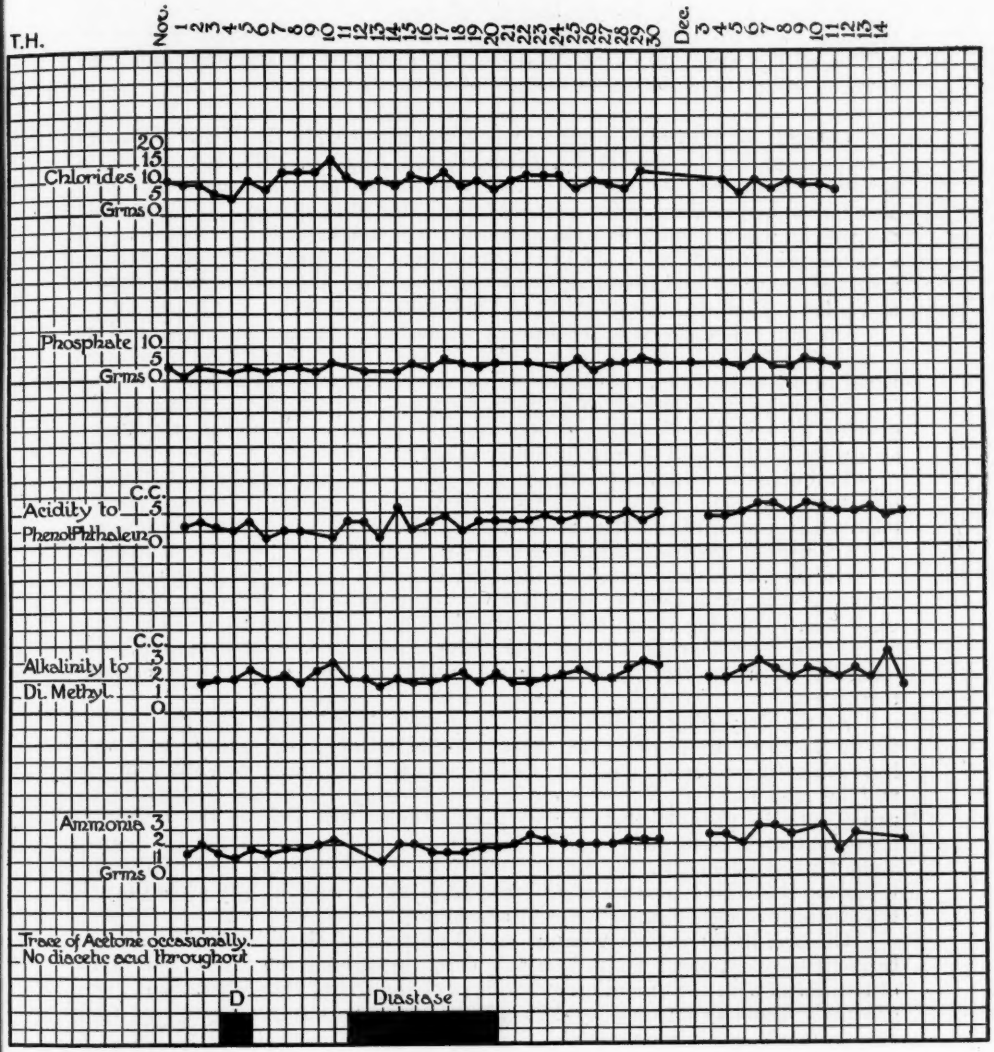


CHART III.

he was given 8 ounces of oatmeal in the form of porridge (portions of this were given every three hours), 8 ounces of butter and green vegetables. Then for two days he was on vegetables, butter, and eggs; and finally, for four days, 10, 8, 6, and 4 ounces of oatmeal (with butter and vegetables as before) were taken respectively. At the end of this period the urine was sugar-free (March 6) and

remained so until his discharge from hospital. The urine was examined at frequent intervals and remained sugar-free until March 19, no more oatmeal being given. It will thus be seen that the diastase for a period of many weeks had little if any effect beyond a slight beneficial one on nitrogen and fat absorption, as mentioned above, whereas two periods only of the 'oatmeal cure' rendered him sugar-free.

In Chart III it will be seen that the diastase had no effect on chloride and phosphate excretion, but that there was associated with it a slight rise in the acidity of the urine to phenolphthalein, the alkalinity to dimethyl-amidoazobenzine, and a slight rise in the amount of ammonia excreted.

Case II. J. H., female, aged 19 years, was admitted to the Royal Infirmary, Liverpool, under the care of Dr. Bradshaw, on Aug. 28, 1911, complaining of thirst and weakness. Up to May of that year she had always been quite healthy. Her father had suffered from gout, and one sister from chorea. In May, 1911, her weight was 8 stone 7 lb. On admission her weight was 6 stone 3 lb. For a month prior to admission she had suffered from indigestion. In May she had a shivering attack, and from that time she noticed that she was becoming thinner and suffered from continuous thirst and polyuria.

On admission she was moderately nourished, not anaemic, and had no symptoms other than thirst and a feeling of weakness. There were no changes found in the respiratory, circulatory, alimentary, or nervous systems.

The urine was passed in amounts of about 100 ounces per diem, specific gravity 1034, and the total sugar was over 100 grammes. Acetone and diacetic acid were both present in large quantity (Chart IV).

Full diabetic diet was given, together with 1 ounce of brandy and 10 grains of sodium bicarbonate three times daily. With this treatment the sugar excretion fell to an average of about 50 grammes per day, the polyuria and thirst disappeared. The amounts of acetone and diacetic acid still remained high, also the ammonia.

On Nov. 3 a preparation of diastase, obtained by precipitating a watery extract of malt with alcohol, was given in watery solution. This was continued until Dec. 10, during which time observations on metabolism were made daily. It will be seen that no change was brought about in sugar excretion. The quantity of urine remained the same, and the urea output was constant throughout.

At the beginning of November the sodium bicarbonate was increased to 20 grains three times daily, as the ammonia, acetone, and diacetic acid were increasing in amounts. On Nov. 14 the sodium bicarbonate was stopped. As will be seen in Chart V, there was a rise following this in the reaction of the urine both to phenolphthalein and to dimethyl. The rise in the acidity to phenolphthalein was due to this change; but, as is seen in the later cases, a similar though smaller rise in the acidity to phenolphthalein is to be observed following the administration of diastase preparation without any alterations in the amounts of either ammonia or of organic acids.

On Dec. 10 the patient was put on 0·3 gramme of Merck's absolute diastase three times daily, and remained on this drug throughout the rest of the period of treatment with the exception of ten days at the end of December. The sugar gradually came down, and by Feb. 17 the urine was sugar-free to all tests. The ammonia was almost normal, the alkalinity to dimethyl was as low as at the beginning of the experiment, but the acidity to phenolphthalein remained high. Acetone and diacetic acid had completely disappeared from the urine by Jan. 23.

The urine remained sugar-free until March 13. On this and subsequent days 2 ounces of bread were allowed daily. The sugar reappeared on March 27, and on that date there was diarrhoea, which was controlled by the administration of bismuth carbonate. The bread was stopped on April 10, but the sugar still

continued as high as 2 per cent., the patient being on diastase throughout. On April 17 an oatmeal course was given and the sugar dropped on the 23rd to 0·6 per cent., the quantity of urine remaining about the same. The patient

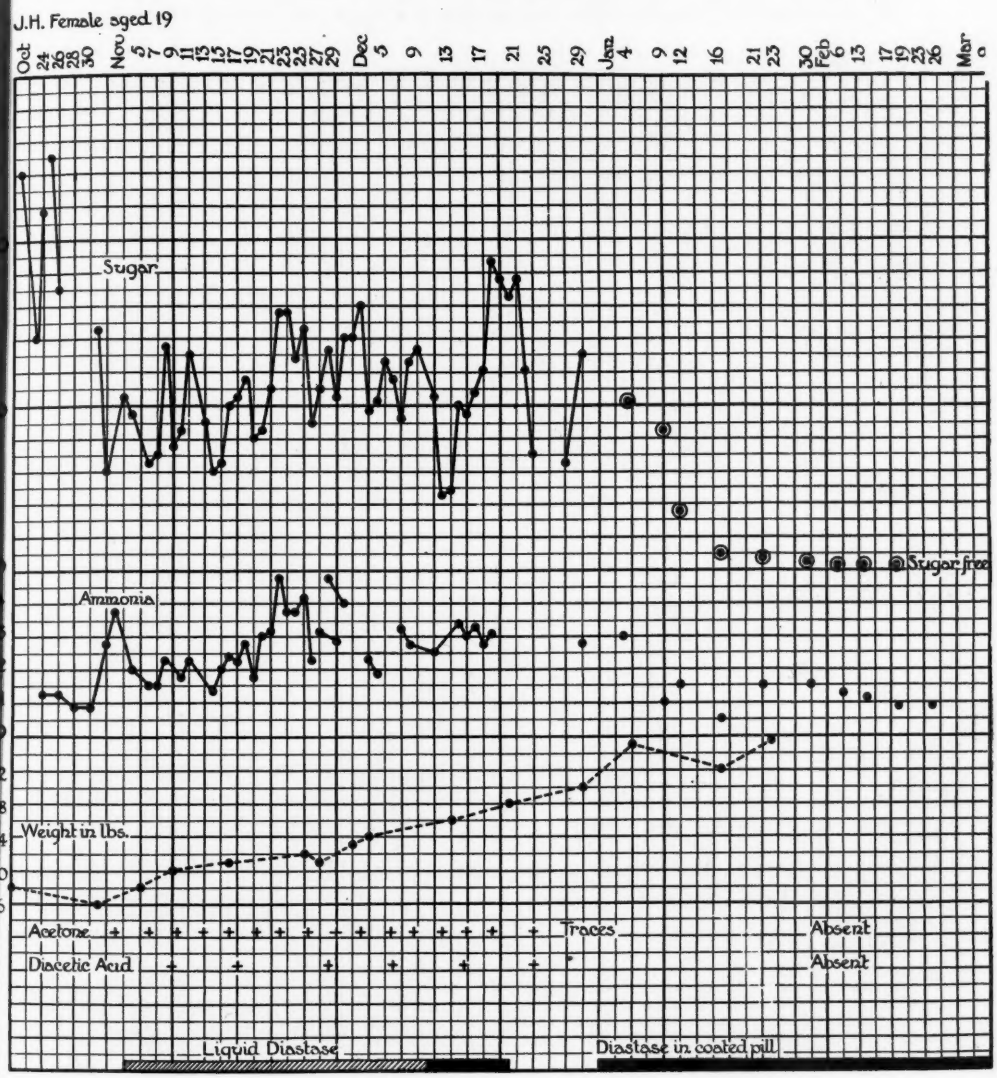


CHART IV.

was out of hospital and at work, so that the quantity passed could not be accurately measured.

This case was treated with diastase for a period of five months, but there appears to be little evidence that it caused the disappearance of the sugar, as even after all these months' treatment the patient had no tolerance for bread. She responded to oatmeal in April, though not so completely as Case I. We

think, therefore, that the response to oatmeal could not be attributed to a diastase ferment or corresponding zymogen present in the oatmeal.

Case III. W. R., male, aged 31 years, was admitted under the care of Dr. Bradshaw on Sept. 26, 1911, complaining of hunger and marked weakness in

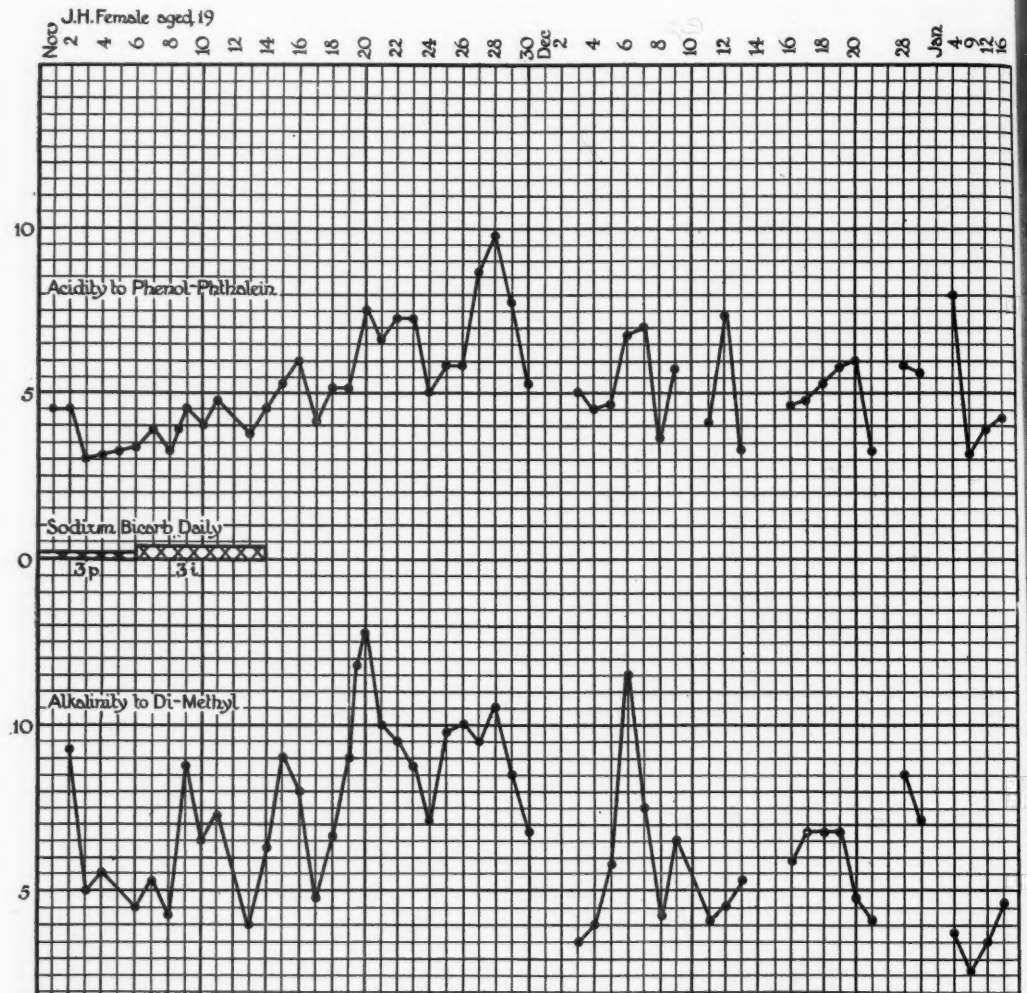


CHART V.

his legs. There was no history of any previous illnesses and nothing of import in the family history. He stated that he was quite well until six weeks before admission, when he had an acute illness associated with diarrhoea and vomiting. During these six weeks he lost 14 lb. in weight, and was unable to eat any food, as the least amount caused him to vomit. The vomiting lasted about two weeks,

and afterwards he had great thirst, sleeplessness, and night-sweating. On admission he was very thin, the cheeks were sunken, and the face had an anxious expression. The pulse rate was 72 per minute, and of poor volume and tension; the temperature was normal, the skin moist, the tongue very red and

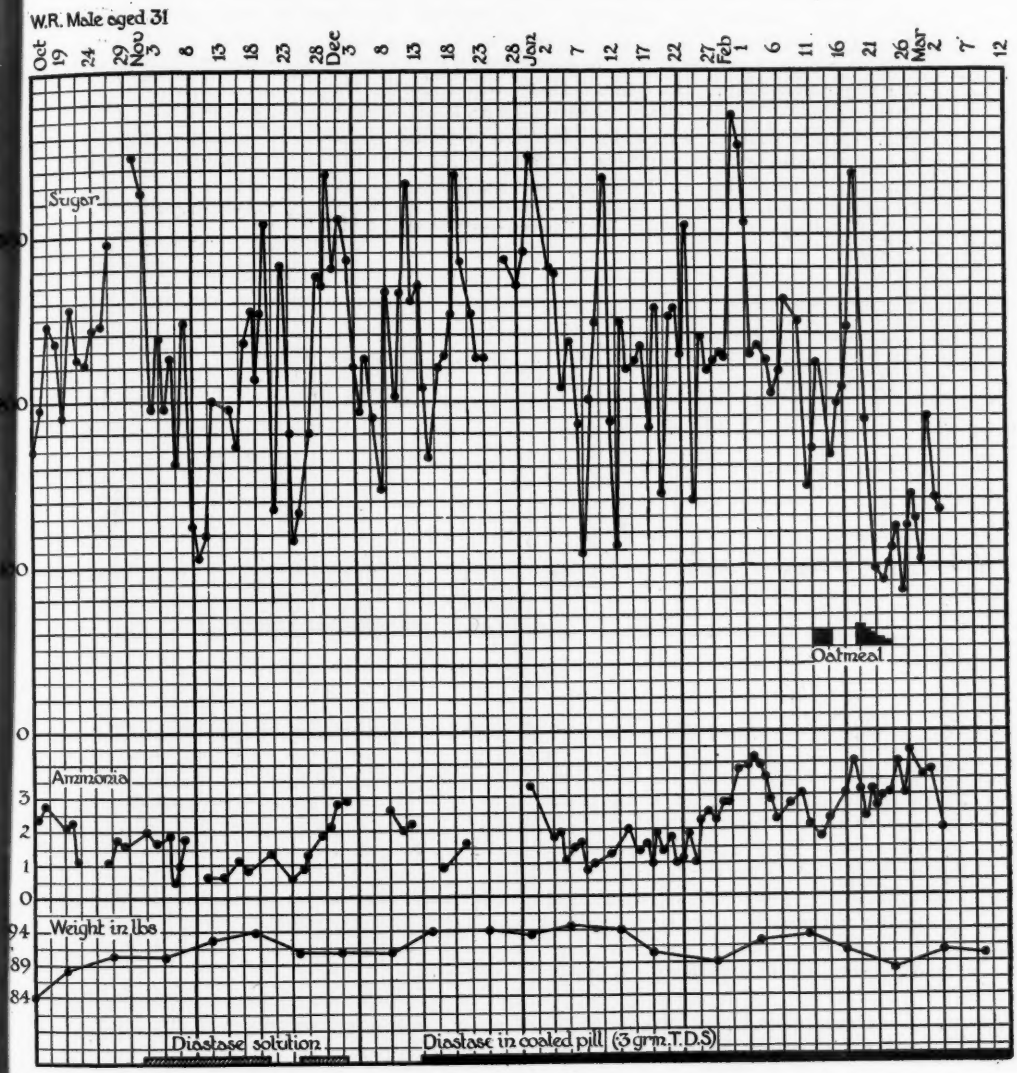


CHART VI.

raw; the stomach was enlarged, reaching on percussion to the level of the umbilicus; both recti were rigid. At the right apex there was increased vocal resonance both in front and behind, and harsh breathing was heard at the left apex. Our observations commenced on Oct. 14.

As will be seen from Chart VI the sugar output was extremely irregular

throughout the whole period he was in hospital, this being possibly due to his not adhering strictly to the diet ordered. At the beginning of November the acetone, diacetic acid, and ammonia were all very high. There was a low acidity to phenolphthalein (Chart VII).

Throughout the whole of the period he was in hospital acetone and diacetic acid were present in quantity. No sodium bicarbonate was given. On Nov. 1 a solution of diastase, which we prepared from malt, was given, and this was continued until the beginning of December. There was no effect on the sugar excretion. On Dec. 23 there was a rise in the acidity and alkalinity of the urine to the indicators mentioned, and also in the ammonia output. On Dec. 12 the patient was given Merck's absolute diastase in coated pills of 0·3 of a gramme three times a day; the acidity of the urine continued at the same high level, but in February the ammonia output still further increased. During December and January the alkalinity to dimethyl was very low.

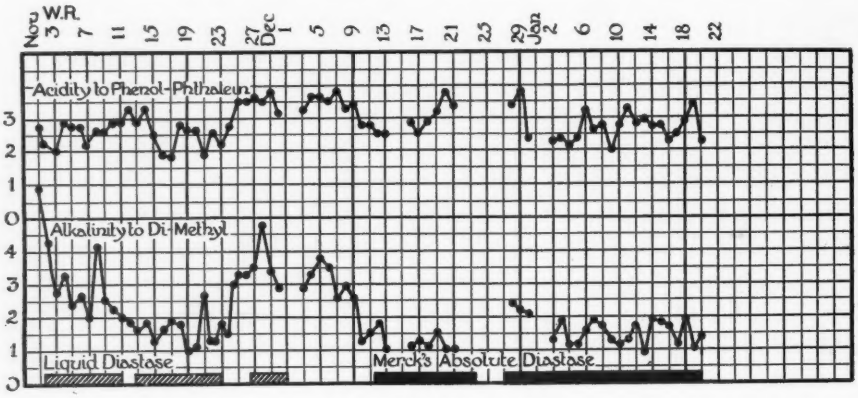


CHART VII.

By Feb. 11 the patient had developed some definite signs of phthisis at both apices. The sugar output continued at a very high level, and the patient's general condition was no better than on admission. On this date a course of oatmeal was commenced, being preceded by two days on which the diet consisted chiefly of vegetables, and followed by three similar days as advocated by von Noorden. This was followed a week later by a second course of oatmeal, and on Feb. 21 and for the following week the sugar output was lower than at any time during the previous six months. The patient therefore responded slightly to the oatmeal, and it is obvious from the chart that the effect produced by the oatmeal was not due to a diastase ferment contained in it, as he had been on a preparation of diastase for a prolonged period.

Case IV. C. M., male, aged 45 years, was admitted on Aug. 9, 1911, under the care of Dr. Buchanan, complaining of frequency of micturition, loss of weight, and thirst. These symptoms had persisted for two years. He was a poorly nourished man, pale, with a very dry skin. He had suffered from severe sweating for the past month. His weight was 110 lb. There was marked constipation. No physical signs of phthisis could be detected. The abdomen was slightly distended and inelastic. The sugar excretion varied from 170 to 220 grammes per day. He was put on a strict diabetic diet and 5 grains of takadiastase three times daily.

Our observations were commenced on Sept. 25, at which time he was

passing 100 grammes of sugar daily, and his weight was 124 lb. Daily observations were made as shown in Charts VIII and IX.

This patient having been on takadiastase for a period of five weeks, careful observations were made on metabolism during the sixth week on the drug.

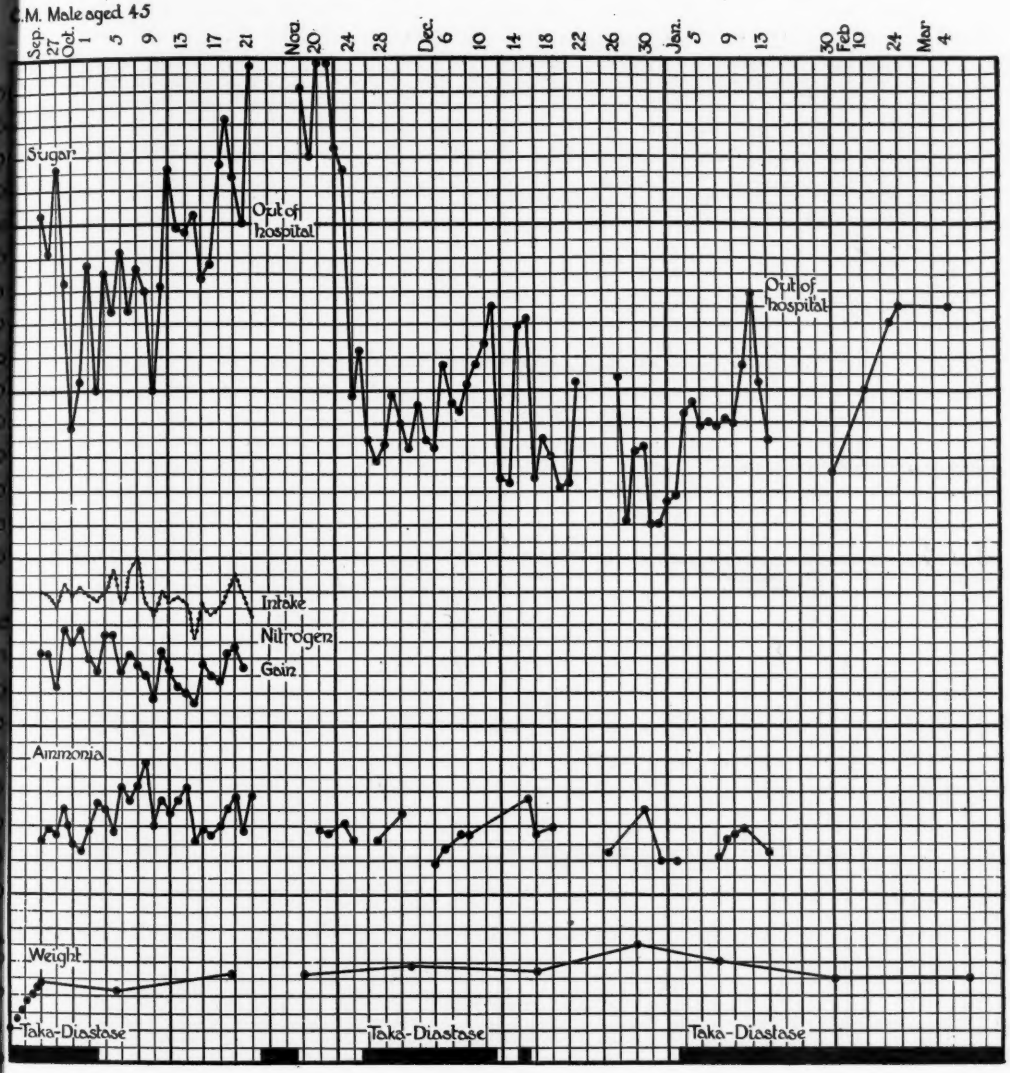


CHART VIII.

Then on Oct. 2 the diastase was stopped. As will be seen from the charts, the following three weeks showed a rise in the sugar output and a slight fall in the nitrogen gain. This fall in the nitrogen gain is to be associated with and closely follows the fall in the nitrogen intake. The withdrawal of the takadiastase was

followed by no change in fat absorption. The sixth week on diastase showed an average fat absorption of 95·8 per cent. The following three weeks, when no diastase was given, the average absorption was 95·6, 94·5, and 97·6 per cent. respectively. Charts VIII and IX show his subsequent progress with taka-diastase given at various periods. There appears to be no relation between the

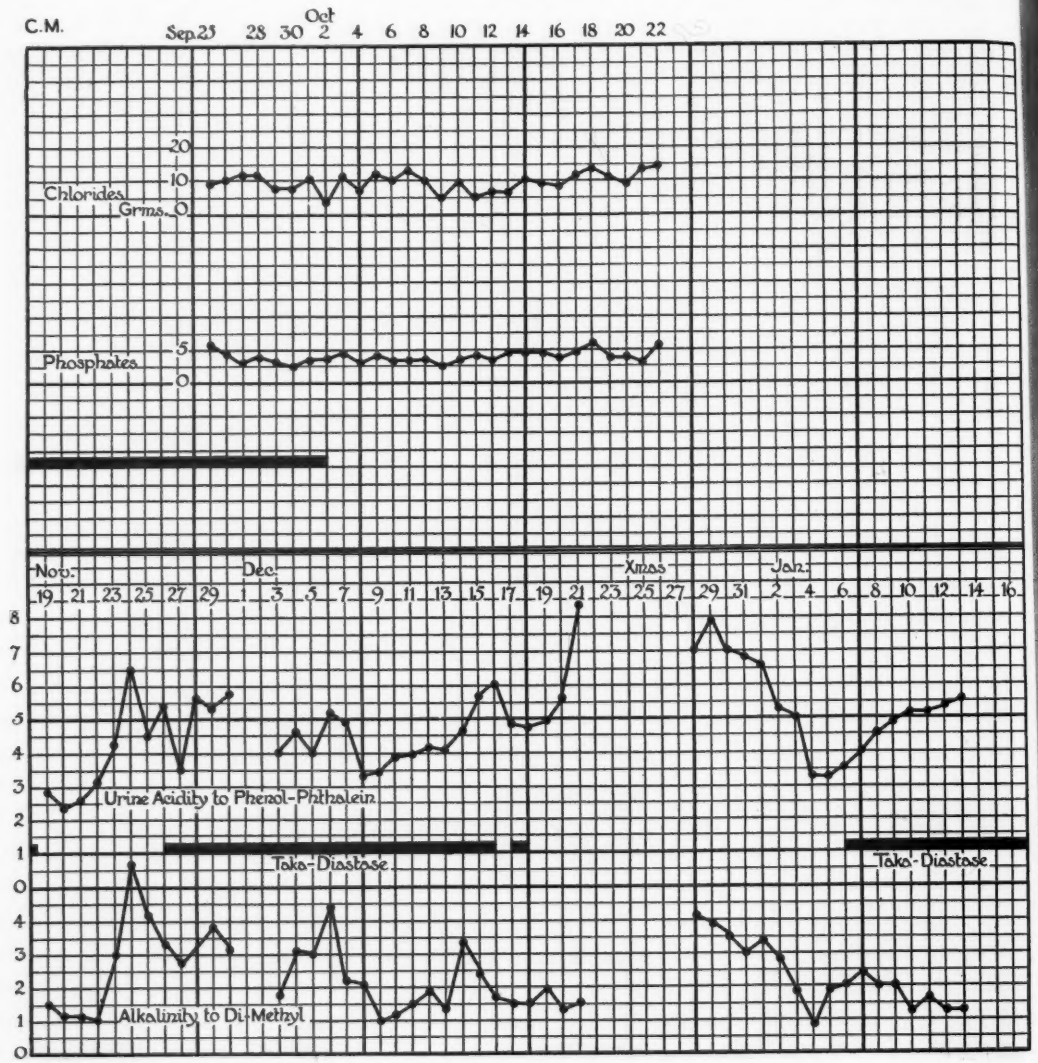


CHART IX.

sugar and ammonia excretion and the giving or withdrawal of the drug. Chart IX shows no change in the chloride or phosphate excretion when the drug was withdrawn after a period of six weeks' administration, but a slight rise is to be seen in the acidity of the urine coincident with its administration. No sodium carbonate was given.

He left hospital on Jan. 13, the urine being small in amount and containing about 60 grammes of sugar per day; the ammonia output was low, and only faint traces of acetone and diacetic acid were present. He attended at the Out-patient Department at various intervals, and during this time the sugar increased in amount. He continued taking Merck's diastase all the time he was out of hospital. It was discontinued on his readmission on March 14. He felt well for three weeks after leaving hospital, then his legs began to swell, weakness and thirst became marked, and the diarrhoea, from which he suffered when in hospital before, still continued. He had palpitation and dyspnoea, and the urine was much diminished in amount.

On admission he had orthopnoea, marked oedema of the legs and back. The abdomen was slightly distended. Diarrhoea still continued although he was not taking diastase, which he thought had caused it before. The sugar had increased in amount on March 19 to 107 grammes, acetone and diacetic acid were present in quantity, but the ammonia secretion was not very high. Crepitations were heard over various parts of the chest, especially at the margins on the right lung in front and at the bases. The heart was irregular and feeble. He was kept in bed on strict diabetic diet, but the sugar excretion remained high. On March 26 and following dates he was tried on von Noorden's 'oatmeal cure', and although the sugar fell on the third day to 20 grammes, it immediately returned to and remained at its former high level. He continued to be troubled with his heart, the sounds being very weak and irregular. There was a systolic bruit at the apex with reduplication of the first sound. Sphygmographic tracings, by Dr. Hay, show irregular fibrillation of the auricle. The oedema had disappeared by March 28, and the weight was increasing. On March 15 he was put on an alcoholic extract of the husk of the meal, and on May 1 was still on it. The patient felt better, had gained in weight, had a much better appetite, and the diarrhoea had disappeared, but the sugar output still remained high and if anything was increasing in amount. The acetone and diacetic acid were still high and the ammonia had increased in amount.

Case V. I. H., male, aged 32 years, was admitted under the care of Dr. Abram on Jan. 24, 1912, complaining of great thirst and weakness, especially in the legs.

His mother has had diabetes for the last seven years, and one brother, who died aged 18 years, had glycosuria following an accident. His past history shows nothing of importance, his only previous illness being malaria.

The frequency of micturition commenced about twelve months before admission. This was accompanied by great thirst and hunger, and the patient became rapidly thinner and weaker. His weight fell from 12 stone 6 lb. to 9 stone. He occasionally had severe attacks of cramp in his legs.

On admission the alimentary, circulatory, and respiratory systems were found to be normal. The nervous system showed absence of knee-jerks and of the superficial reflexes generally, including the plantar. Urine 170 ounces per day, acid, with about 330 to 450 grammes of sugar (Chart X).

He was given strict diabetic diet, but the amount of sugar still remained very high. On Feb. 5 and the four following days oatmeal was given in the usual way, and the amount of sugar became lower than at any period. On Feb. 11, 12, and 13 he was given oatmeal, and while he could tolerate 12 ounces he was unable to tolerate 16 ounces given on the third day. As this patient complained bitterly of the diet, oatmeal was given on Feb. 19 with his usual protein diet. As will be seen from the chart the oatmeal so given was not tolerated and the sugar output was higher than on any previous occasion. Subsequent oatmeal courses without protein were well tolerated, and by the end of March his sugar output was brought down to a level of 40 grammes per day.

He was then given an alcoholic extract of the husk of the meal, but there was no alteration in the sugar output. We found on several occasions that the patient was not adhering to the prescribed diet, and he was therefore discharged from hospital.

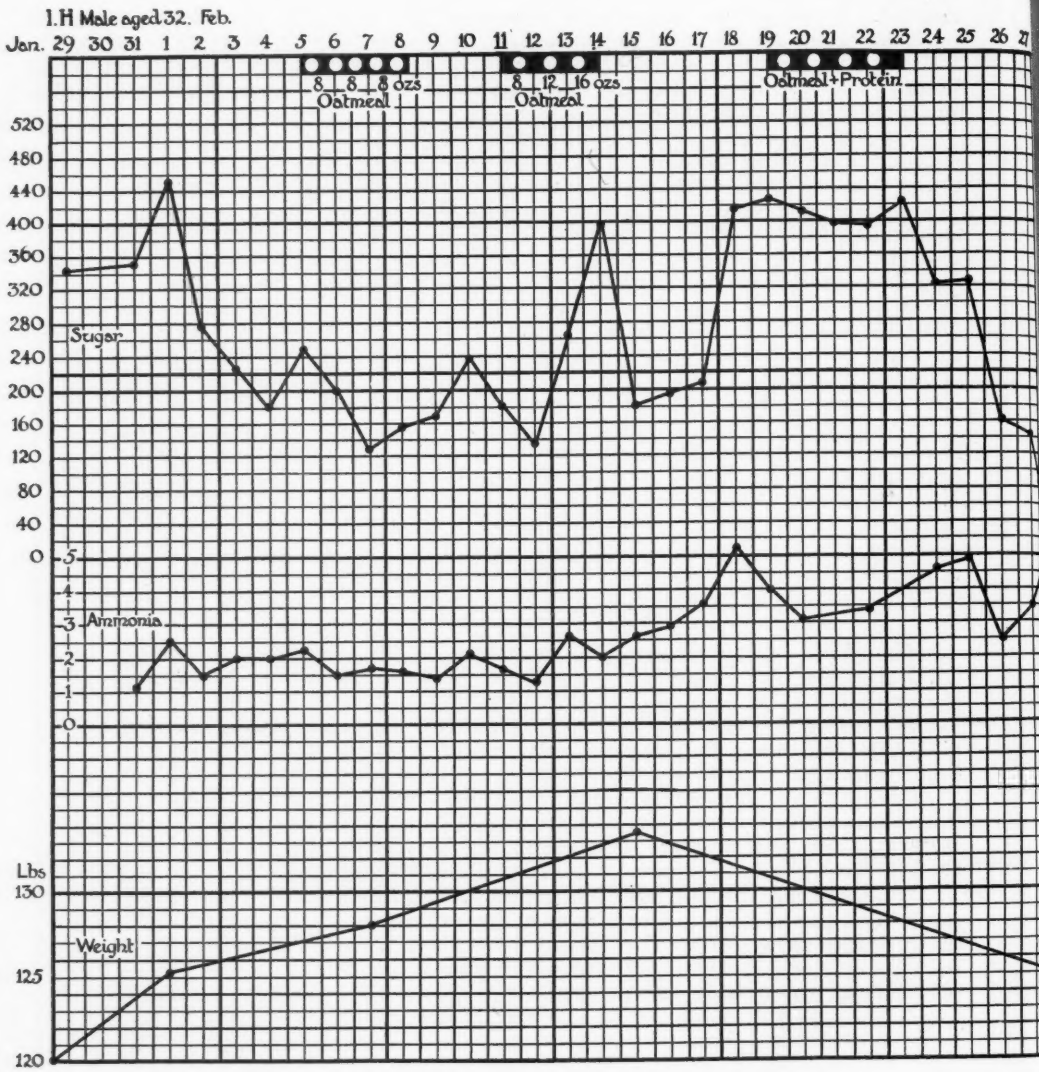


CHART X.

Case VI. C. W., male, aged 45 years, was admitted Oct. 28, 1911, to the Royal Infirmary under the care of Dr. Buchanan, complaining of severe headache, pains in the back and legs, poor appetite, but no thirst.

This patient had been in hospital from April 15 to June 6, 1911. When under the influence of strict diet and codein his sugar gradually dropped from

97·2 grammes per day to 2·4 grammes. During the last month he took takadiastase 5 grains three times a day, and the fall in the sugar continued.

From June to October he attended regularly at the Out-patient Department; he was then readmitted complaining of the symptoms mentioned above. His weight was 9 stone 4 lb., i. e. 2 lb. less than it was when he left hospital in June, his diet having been fairly strict all the time.

On admission he was passing 155 grammes of sugar per day. There was no acetone or diacetic acid and the ammonia output was low. As he was said to have responded to takadiastase when in hospital before, it was decided to try Merck's absolute diastase, the diastatic value of which is higher than that of takadiastase. It was enclosed in the capsules mentioned to protect it from the gastric juice. This was started on Nov. 10, but the sugar output did not vary much, or, if anything, tended to rise slightly. The excretion of ammonia remained about the same. Very slight rises were observed both in the acidity to phenolphthalein and the alkalinity to dimethyl. The patient's weight rose from 9 stone 4 lb. to 9 stone 10 lb. during the time he was in hospital.

He was discharged on Dec. 2, and continued the diastase while attending as an out-patient, the amount of sugar passed remaining about the same. He has since developed signs of phthisis at the left apex.

Case VII. M. McC., female, aged 49 years, was admitted under the care of Dr. Buchanan on Jan. 14, 1912, complaining of frequency of micturition, which was associated with pain. Her mother and one sister died of phthisis. She stated that she had had typhoid fever on two occasions. The frequency of micturition had troubled her for one year prior to admission. She stated that she was always thin, and had always suffered from severe headaches. There was no hunger or thirst. On examination she was found to have a partially compensated double lesion of the aortic valve. The urine was small in amount, only 20 ounces being passed daily. The specific gravity was 1022, and traces of albumin were detected, but no casts. It contained sugar in quantities of about 30 grammes per day. There was no acetone or diacetic acid present, and the ammonia output was only 0·3 gramme per day. With rest the urine increased in amount.

The diet was gradually changed and eventually a strict diet was given. With this diet the sugar excretion was higher than on admission, reaching as much as 40 grammes per day.

On Jan. 26 Merck's diastase in coated capsules was given and continued throughout her stay in hospital. In the following eight days there was no change in sugar excretion. On Feb. 4 an oatmeal course was started. By the 12th the sugar excretion was only 7 grammes per day, and by the 22nd it was as low as 3 grammes per day. On this date there was a trace of acetone. She was then given a diabetic diet and the sugar again rose, reaching as high as 50 grammes per day. The patient left hospital on March 9, and has not since been under observation. During the whole of this later period in hospital she was taking diastase, which obviously had no effect in any way comparable to the oatmeal course.

Other Cases. In addition to the above cases, we have had under observation nine other cases for various periods in the Out-patient Department. In these cases the urine was examined twice weekly, the sugar and ammonia being estimated. It was found impossible to get the quantities of urine noted with any degree of accuracy. The cases varied from 12 to 60 years of age, and were all true diabetes. They were all given diastase in one of the forms mentioned in the former cases, mostly Merck's absolute diastase.

In none of them was the response to oatmeal tested. The sugar excretion has been noted in the various cases in periods of from one month to as long as

six months. In none of the cases have we been able to observe any effects which could be attributed to any other cause than that of the diet. In no case can we find any evidence that the diastase given has influenced the sugar excretion.

Conclusions.

In the prolonged daily study of cases of diabetes treated with diastase we have been unable to observe any beneficial effects which could be attributed to it.

In cases which responded markedly to a course of oatmeal given as advocated by von Noorden, no such effect can be obtained by any preparation of diastase we used.

If there is any specific body in oatmeal which has an effect on carbohydrate metabolism, it is not a diastase ferment.

We wish to express our indebtedness to Professor Benjamin Moore for much valuable advice, to Drs. Bradshaw, Abram, and Buchanan for the full and unrestricted facilities they have given us for conducting these observations, and to Drs. Holland and Hay for their observations which are recorded above.

REFERENCES.

1. Beardsley, *Therap. Gaz.*, 1911.
2. Wakeman, *Med. Record*, 1911.

THE ACTION OF THE VAGUS ON THE HUMAN HEART

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With Plates 1–8

Methods of Examination.

THE results obtained from a clinical study of the action of the vagus on the human heart are recorded in this paper. The investigation, which was carried out in the Clinical Medicine Research Laboratory of the Edinburgh Royal Infirmary, was undertaken with two main objects in view—firstly, to determine whether paresis and compression of the vagus induce the same effects on the human heart as on the lower mammalian heart, and, secondly, to ascertain whether these effects can be of service in diagnosis, prognosis, or treatment.

In order to induce a partial and transient paralysis of the vagal endings in the heart, 0·02–0·03 grain of atropin sulphate was injected subcutaneously. To stimulate the nerve, digital compression, the method originally employed by Czermak (10) and later by Thanhoffer (65), Wasilewsky (73), and Cardarelli (4) was applied, usually for about five seconds, to the surface of the neck over the carotid artery and vagus nerve at about the level of the cricoid cartilage. In each instance firm pressure was applied, but the precise degree of pressure doubtless varied in individual tests. Luciani (43) speaks of vagus compression as an *experimentum periculosum*, since it may produce disquieting symptoms of syncope. In the memorable case recorded by Thanhoffer (65), bilateral compression of the vagi caused a prolonged standstill of the heart accompanied by an epileptiform seizure. I have applied bilateral compression only in cases of complete heart-block and of paroxysmal tachycardia. In but one case of my series did compression of the right vagus, causing arrest of the ventricles for more than seven seconds, produce a sensation of faintness. In no other instance was compression of right, left, or both vagi accompanied or followed by any alarming symptoms. But although the human heart usually begins to escape from vagus inhibition during the period of compression, I have observed cases in whom the inhibitory effects on the ventricles did not cease until after withdrawal of pressure from the right vagus, and in these instances a more prolonged application of the pressure might conceivably have led to syncopal or epileptiform attacks.

[Q. J. M., Oct., 1912.]

The observations were recorded by means of Mackenzie's ink-polygraph, the Knoll-Hering polygraph, or the Cambridge model of Einthoven's string-galvanometer. If a continuous record of the heart's action over a long period was desired, the ink-polygraph was employed, the jugulo-carotid pulsations being recorded together with the apex-beat or the pulsations in the brachial artery. It is usually difficult to obtain satisfactory records of the jugulo-carotid pulsations during compression of the right vagus; but in some patients, especially if they be lying somewhat on their left side, satisfactory records both of the auricular and the ventricular contractions can be obtained from the apical impulse. In cases of auricular fibrillation an apical tracing is preferable to a sphygmogram, because some of the ventricular beats may fail to produce pulse waves in the artery. The contractility of the ventricular musculature, however, can be gauged better from the sphygmogram than from a cardiogram, for the height of the individual beats in the latter may undergo considerable distortion in one or other of the phases of respiration. For recording the effects of vagus compression, the string-galvanometer is better in many respects than a polygraph, particularly as the former instrument furnishes more reliable and instructive records of the auricular beats.

It is well known that not only in all cold-blooded animals but also in the cat, dog, rabbit, guinea-pig, and other mammals the primary effects of vagus stimulation are more pronounced on the auricle than on the ventricle or on the tissues forming the functional bond of continuity between these chambers. Gaskell (26), summing up the effects of vagal stimulation on the auricles, says, 'Such then are the primary effects of stimulation of the vagus nerve: depression of rate, depression of excitability, depression of contraction force, depression of conductivity, depression of tonicity and increased positivity of the muscular substance.' The classical researches of MacWilliam (51), followed by those of Roy and Adami (63) and of Bayliss and Starling (1), have demonstrated that in the mammalian heart vagus excitation may slow or even arrest the auricles, may depress the excitability, contractility, and conductivity of the auricular muscle, may impair the propagation of stimuli from auricles to ventricles, and further may cause ventricular standstill, depress the contractility, and prolong the contraction of the ventricular muscle. In the mammalian heart, vagus stimulation either fails wholly to depress the excitability of the ventricular muscle or produces only a slight degree of depression not at all comparable to the depression of excitability in the auricle.

As atropin depresses or paralyses the vagal nerve endings in the heart, and cuts off the tonic inhibitory influence of the vagus, the effects of the drug should be the reverse of those induced by vagus stimulation. Dixon (14) states that as a result of stimulation of the medulla by the drug we should expect to obtain a slower pulse, but he expressly states that 'this effect is neutralized completely by the peripheral paralysis of the vagi, nevertheless some cardiac slowing is seen occasionally in man soon after an administration of atropin, but is at most very transient'. The results of my own observations may now be considered.

Examples of Ineffective Vagus Compression.

The effects of vagus compression in man are not identical in all instances. In some patients no alteration of rate is observed during compression either of the right or left vagus. Among such individuals there were some in whom the heart was healthy, others in whom there was valvular disease; some were young, others were old. A few illustrative cases may be mentioned.

1. Mrs. M., aged 38, suffering from chronic gastric catarrh, and presenting no cardiac symptoms. Pressure was applied over the right, and subsequently over the left vagus, while electro-cardiograms were being obtained by derivation II. The following periods remained constant before, during, and after compression of the vagus: Ventricular systole (*R* to end of *T*), 0·31 sec.; ventricular diastole, 0·42 sec.; auricular systole, 0·105 sec.; *P–R*, 0·140 sec. Neither right nor left vagus compression was associated with any alteration in the form or height of the deflexions *P*, *R*, and *T*, while the deflexions *Q* and *S* remained inconspicuous throughout the records.

2. In a man, 30 years of age, convalescing from acute lobar pnuemonia, the time interval between successive *R* summits (0·63 sec.) and the *P–Q* interval (0·14 sec.) remained constant both before and during right vagus compression. The deflexions *P*, *Q*, *R*, and *T* underwent no change; the deflexion *S* was absent throughout.

3. Painter's labourer, aged 42 years, suffering from aortic incompetence. Before, during, and after compression of the right vagus, the intervals *R* to end of *T* (0·42 sec.), *P–R* (0·14 sec.), *R–R* (0·73 sec.) remained constant, and no change occurred in the summits *P*, *R*, *S*, and *T*. The deflexion *Q* was absent throughout.

4. Mrs. B., aged 37, suffering from aortic and mitral incompetence. The vagus was compressed eight times on the right and seven times on the left side, while a continuous record was taken with ink-polygraph. No change in the frequency or amplitude of the pulse in the brachial artery was detected beyond a phasic variation, probably of respiratory origin, in the amplitude of the pulse beats after withdrawal of pressure from the left vagus.

5. In a girl, aged 18, suffering from aortic and mitral incompetence, and with a rhythmic pulse of 142 per minute, neither right nor left vagus compression had any influence whatever on the rate, rhythm, or force of the pulse. The girl died about a week later. Similar negative results have been obtained in other cases of advanced valvular disease with a pulse of frequent rate, and either rhythmic or wholly irregular.

6. Charwoman, aged 45, suffering from mitral stenosis. The intervals *R–R* (0·66 sec.), *P–R* (0·14 sec.), the duration of auricular systole (0·10 sec.), and of ventricular systole (0·32 sec.) remained constant before and during right vagus compression; and no change occurred in the form of the deflexions.

7. Labouring man, aged 38, suffering from aortic and mitral incompetence. Before, during, and after compression of the right vagus, the interval *P–Q*

(0·17 sec.) remained constant. Before compression, the interval *Q–Q* was 0·70 sec., and it did not increase beyond 0·80 sec. during or after compression. During compression of the left vagus, the interval *Q–Q* lengthened only from 0·77 to 0·84 sec., while the interval *P–Q* (0·17 sec.) remained unchanged. The form of the deflexions *P*, *Q*, *R*, *S*, and *T* remained unaltered by compression either of right or left vagus.

In many individuals, however, vagus compression produces well-marked effects. In most instances these differ according as compression is applied on the right or on the left vagus. Differences between the effects of right and left vagus compression have been demonstrated in animals by Meyer (53), Gaskell (23), Wesley Mills (77), Hering (31), Rihl (58), Rothberger and Winterberg (61), Flack (21), Garrey (22), and Cohn (5); and in man by Czermak (10), Rihl (59), and Robinson and Draper (60). The right vagus has usually been more effective than the left in slowing the heart, and in the case of bradycardia recorded by Danielopolu (12) the right vagus was compressed by large glands in the neck, while the left vagus was free. I have found that compression of the left vagus in man is frequently ineffective in inducing any change of rate, excitability, contractility, or conductivity in any part of the heart. Compression of the right vagus more often produces effects which are frequently pronounced, and which are closely comparable to, if not wholly identical with, those described by MacWilliam (51) in the heart of the cat and other mammals under vagus stimulation. Moreover, the effects of right vagus compression in man are almost uniformly the reverse of those induced by atropin. These various effects may now be considered.

Effects on the Auricles.

I. *Rate.* (1) *Compression of vagus.* In man, compression of the vagus may lengthen auricular diastole, and thus retard the rate of the whole heart (primary negative chronotropic effect). In this respect the right vagus is almost invariably more effective than the left. In no instance have I observed auricular retardation to be preceded by auricular acceleration, and in this respect the chronotropic effect of vagus compression in man is identical with that of vagus excitation in the frog, tortoise, and eel, and in the rabbit, cat, dog, and other mammals. The degree of auricular slowing during vagus compression varies considerably in different persons. In some the retardation is slight even during firm compression of the right vagus, and wholly, or almost entirely, absent during compression of the left vagus. In other cases a striking retardation can be induced by right vagus compression (Figs. 1, 2, 4, 5, 6, 8, 10, and 19), although only a slight, yet evident, retardation is effected by compression of the left vagus, or although the left vagus may be ineffective (Fig. 3).

The striking difference in the rate and contractility of the auricles that usually ensues on compression over the right as compared with the left vagus, indicates that the effects produced on the heart by means of the compression are

not due to mere compression of the neighbouring great vessels. Again, it can be shown that compression of other great vessels, such as the brachial or femoral artery, does not inhibit the heart as compression of the right vagus does. And further, the effects of compression applied to the neck cannot be attributed to elevation of blood-pressure, for the fall in the arterial tracing during a standstill of the heart that has been induced by compression of the right vagus (Fig. 19) indicates a fall of systemic blood-pressure, such as we know occurs in the dog during the period of vagus stimulation.

The apical tracing in Fig. 15, obtained from a woman aged 45 and suffering from mitral stenosis and incompetence, illustrates some of the lesser effects of right vagus compression. The interval between successive ventricular systoles lengthens from 0·68, 0·68, 0·70, 0·70 sec. before compression of the right vagus to 0·71, 0·76, 1·00, 0·88, 0·88, 0·90 sec. during the compression period, and shortens to 0·88, 0·88 sec. after the pressure was withdrawn. As the duration of auricular systole and the *As–Vs* interval remain constant at 0·088–0·10 sec. before and during the test, and as the duration of ventricular systole, as far as can be determined, remains constant throughout, the retardation of the whole heart during compression of the vagus must be ascribed to lengthening of auricular diastole. I do not propose to discuss whether this lengthening of auricular diastole is the manifestation of a primary effect on stimulus production in the auricle, on the excitability, or on the refractory period of the auricular muscle. It is evident, however, that, as was demonstrated by Czermak (10), the rate of the human heart may be retarded by vagus compression in a manner strictly comparable to, although of lesser degree than, the 'depression of rhythmical power' (Gaskell, 26) in the auricle of the tortoise and frog, and to the depression of 'inherent rhythmic power' in the auricle of the eel (MacWilliam, 50) under vagus stimulation.

Marked lengthening of auricular diastole is demonstrated in Figs. 1 and 4. The electro-cardiogram in Fig. 1 was obtained by derivation II (right hand and left foot) from a miner, aged 43, suffering from chronic nephritis. The right vagus was compressed during the period indicated by the electric signal. Before compression the auricular diastole lasts 0·63 sec., whereas the first auricular diastole after the commencement of compression lasts 0·77 sec., the second lasts 1·15 sec., the third 1·36 sec., the fourth 1·12 sec., and the fifth 1·01 sec. The succeeding auricular systole coincides with the release of compression, and thereafter the successive auricular diastoles shorten still further. During compression of the left vagus the maximal lengthening of auricular diastole was from 0·66 to 0·77 sec. The degree of auricular retardation in Fig. 4, from a man aged 53, is much the same as in Fig. 1, for before compression of the right vagus auricular diastole lasts 0·66 sec., while the longest auricular diastole during the compression period is 1·22 sec.

A more pronounced auricular retardation is shown in the electro-cardiogram of Fig. 2, obtained by derivation II and during compression of the right vagus from a labouring man, aged 40, suffering from carcinoma of the oesophagus. In

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this record the auricular diastoles before compression were 0·80 and 0·84 sec., whilst the longer of the two complete auricular diastoles during the compression period lasts 2·31 sec. During compression of the left vagus there was no slowing of the heart, nor any change in the form or relative position of the deflexions *P*, *R*, *S*, and *T* (Fig. 3).

In Figs. 8, 9, and 19 a prolonged standstill of the whole heart ensues on compression of the right vagus. In Fig. 8 auricular diastole persists for 4·44 seconds, and for nearly four seconds in Fig. 19. The effects that I have obtained by compression of the right vagus are similar to those recorded by Wenckebach (76) and Laslett (40) in the human heart, and by Rothberger and Winterberg (61, 62) in the dog's heart under vagus stimulation.

In the human heart the latent period of vagus inhibition—the period elapsing from the application of pressure on the nerve until the first manifestation of depression of rate or contractility—is of variable length, but usually one, and sometimes two, auricular beats of normal rate and strength occur before either their rate or force becomes lessened. The duration of the latent period in Fig. 2, where right vagus compression commenced during a ventricular systole, is longer than that in Fig. 1, where vagus compression commenced during an auricular systole. That the duration of the latent period varies according to the phase of the cardiac cycle at which stimulation is initiated was pointed out by Czermak (11). Whether the difference between the latent periods in Figs. 1 and 2 is due to this cause, or whether the full compression was applied more suddenly in Fig. 1 than in Fig. 2, I am unable to state. The vagus effect, whether on rate or contractility, or on both, is attained gradually, and subsides gradually either while the pressure is still being maintained or not until after the pressure has been withdrawn.

(2) *Atropin.* An illustration of auricular acceleration (primary positive chronotropic effect) induced by atropin is shown in Fig. 23. The curves were constructed from a continuous record taken by means of the ink-polygraph from a man, aged 62, who presented complete auriculo-ventricular dissociation. The auricular rate was 87·5 per minute before the subcutaneous injection of 0·02 grain atropin sulphate. In three minutes the auricular rate had fallen to 81, in six minutes it had risen to 88, in nine minutes to 97, and in twenty minutes to 101 per minute. A pronounced initial retardation of auricular rate, followed by acceleration, is shown in Fig. 24. This test was performed on a man, aged 45, presenting digitalis heart-block. On the day when the test was performed the auricular rate varied from 83 to 85 per minute. The subcutaneous injection of 0·03 grain of atropin sulphate caused an initial retardation of auricular rate to 75 per minute. This retardation passed off at the end of seven minutes, and was followed by a progressive acceleration attaining a maximum of 107 per minute twenty minutes after injection of the drug. From the twenty-first until the thirty-seventh minute an auricular rate of 101 to 107 was maintained, rising to 120 when the patient rose up from the couch at the forty-second minute.

It is thus evident that the initial effect induced by 0·02–0·03 grain of atropin sulphate may be auricular retardation lasting for six or seven minutes. This is followed by acceleration which is due to shortening of auricular diastole.

II. *Excitability.* (1) *Compression of vagus.* Physiologists have demonstrated that excitation of the vagus in animals depresses the excitability of the auricular muscle (primary negative bathmotropic effect). Gaskell (26) states that this effect 'is now universally allowed'. It is usually difficult to estimate the excitability of the auricular muscle in man. The methods applied by the physiologist to determine the threshold of excitability are not applicable to the human heart. The only criterion which permits the clinician to assume that the excitability of the human auricle is increased is the occurrence of supra-ventricular extra-systoles, and even these indicate the presence of one or more unduly irritable foci in the auricular wall rather than of a general increase of excitability throughout the auricular muscle. An increased rate of auricular contraction is still less reliable evidence of heightened auricular excitability, because acceleration of rate may be due to other causes, for example, quicker rate of stimulus production, or shortening of the refractory period.

In my own observations I have never observed any indication of auricular excitability being increased during compression of either vagus, nor have I observed changes which indicated definitely a primary depression of auricular excitability. In two instances, however, there was evidence of increased excitability as an after-effect. Reference will be made to this in a later part of the paper (p. 66).

(2) *Atropin.* As excitation of the vagus in animals depresses auricular excitability, atropin, by cutting off the tonic influence of the vagi, ought to increase excitability (primary positive bathmotropic effect). The drug might therefore be expected to cause the appearance of supra-ventricular extra-systoles, or lead to an increase of their number. These effects I have not observed. The absence of any manifest increase of auricular excitability may possibly be due to the acceleration of rate exerting secondarily a negative bathmotropic effect.

In one instance atropin appeared to exert, not a positive, but on the contrary a negative, bathmotropic effect. The patient was a man aged 67, affected with arterial sclerosis, and presenting numerous supra-ventricular extra-systoles. His pulse-rate was 91, with from four to six extra-systoles per minute, before the administration of 0·025 grain of atropin sulphate subcutaneously. For a period of twelve minutes after the injection the heart's rate tended to be slower, and no acceleration of rate occurred until 23·5 minutes after the injection (Fig. 25). The number of extra-systoles per minute fell from 5 in the fourth minute to 0 in the seventh, and only 5 extra-systoles were recorded during the period from the seventh to the nineteenth minute, during which period, however, the record was interrupted for two minutes while a fresh roll of paper was being adjusted to the polygraph. The curves in Fig. 25 indicate that the diminution in the number of extra-systoles was not due to cardiac acceleration, and suggest that atropin may depress the excitability of an unduly irritable focus in the auricle.

In this patient, compression of the left vagus sixteen and a half minutes after the injection of atropin failed to slow the pulse, whereas during compression of the right vagus at the eighteenth minute the pulse-rate fell from 88 to 46. Subsequent compressions of the right vagus were less effective (Fig. 25).

III. *Contractility.* (1) *Compression of vagus.* Physiologists are agreed that vagus stimulation may depress the contractility of the auricular muscle (primary negative intropic effect). MacWilliam (51) expressly points out that depression of auricular contractility is an early and striking effect of vagus stimulation; that it occurs even when the auricular beats are merely retarded—not necessarily arrested—and that both the onset of, and recovery from, depression of contractility are gradual. Engelmann (16) made the same observations fourteen years later.

An identical negative inotropic effect may be observed in the human auricles. In this respect the right vagus is again more effective than the left. Diminution in size of the auricular summit, *P*, is not usually detected in the absence of auricular retardation, yet in some instances there is a pronounced negative inotropic effect with only slight retardation (Fig. 10). Depression of auricular contractility is seldom apparent in human electro-cardiograms until the second beat after the commencement of vagus compression. The succeeding auricular beats may then exhibit further depression of contractility, and the depression may become so great that the summit *P* is extremely small, as in Figs. 1 and 2. In Fig. 4, *P 6* has become so small that it is not visible in the record. After withdrawal of the pressure, auricular contractility as a rule becomes restored gradually, and often is not fully recovered until five or more beats have occurred. The record in Fig. 8, from a miner aged 46, illustrates an exception to this rule, for here the first auricular summit after an auricular diastole lasting 4·44 seconds is not reduced in size.

Examples of diminution in the height of the summit *P*, signifying depression of auricular contractility, in association with auricular retardation, are seen in Figs. 1, 2, 4, 5, and 6. Fig. 10, from a clothier's shopman, aged 55, suffering from mitral stenosis and presenting a loud rough presystolic murmur, shows a pronounced negative inotropic effect on the auricles during and after compression of the left vagus. In this patient compression of the right vagus caused a similar effect. The relation between the height of the summit *P* and the intensity of the presystolic murmur was unfortunately not observed.

Einthoven (15) has recorded electro-cardiograms demonstrating that in the dog during vagus stimulation the summit *P* may not merely be diminished in size, but may be altered in form, for the initial deflexion upwards may be succeeded by a depression which falls below the base line, and only gradually thereafter rises to it again. More recently, Kahn (38) and Rothberger and Winterberg (62) have recorded similar diphasic auricular summits. This alteration of form may be observed in the deflexion *P 5* of Fig. 5.

Under the influence of right vagus compression the form of the auricular deflexion may undergo still further change. Thus in Fig. 1 the second auricular

beat, *P 5*, after the onset of vagus compression, is represented by an initial deflexion downwards followed by a deflexion upwards to the base line in contradistinction to the antecedent auricular deflexions which are of normal form. In Fig. 1 *P 7* presents a double upward summit. In Fig. 6, *P 3* is in part inverted; *P 4* consists of two upward deflexions, the first being succeeded by a fall to the base line, whereas after the second upward deflexion there is a fall below the base line. In view of Lewis's (41) experimental researches on the form of the auricular deflexion associated with primary negativity in different parts of the auricular wall, the alterations in the form of the deflexion *P* during the period of vagus compression suggest that the vagus effect on the auricles is more marked at, or in the vicinity of, the sino-auricular node than at other parts of the auricular wall, and that during the compression period some other part of the auricle than the sino-auricular node may initiate the contraction.

(2) *Atropin.* The administration of atropin in doses sufficient to depress the tonic influence of the vagi ought to increase the contractility of the auricles (primary positive inotropic effect), for Einthoven (15) has shown that after section of both vagi in dogs the height of the summit *P* is increased nearly threefold. In man the positive inotropic effect of atropin cannot be studied satisfactorily except in electro-cardiograms, because the height of the auricular wave in polygraphic tracings is not a constantly reliable index of the strength of the auricular contraction. I have not yet obtained a sufficient number of electro-cardiograms recording the effects of atropin to permit my drawing any definite conclusions regarding the influence of the drug on auricular contractility. In all the tests the tension of the string was adjusted to give a deflexion of 1 cm. for each millivolt of difference in potential applied to the terminals of the string, while a resistance equal to that of the patient was introduced in the galvanometer circuit. The height of the auricular summits in the whole series of electro-cardiograms, obtained before and at intervals after the injection of atropin, may therefore be compared. The height of the auricular summits has remained remarkably constant, notwithstanding the auricular rate being accelerated. It is conceivable that there was a real increase of contractility after administration of atropin, but that this increase was masked by the accelerated rate, and that had the same degree of acceleration not been associated with increased contractility the height of the auricular summits would have been lessened.

IV. *Conductivity. Vagus compression and atropin.* Both Gaskell (23, 25) and MacWilliam (51) have demonstrated that the conductivity of the auricular tissue may be depressed by stimulation of the vagus (primary negative dromotropic effect). Although prolongation of auricular systole cannot be regarded as definite proof of depressed conductivity in the auricular walls, it may be due to such depression. Einthoven (15) has recorded that the duration of auricular systole in the dog may be slightly prolonged by stimulation of the right vagus and slightly shortened by section of the vagi. I have records of only one human heart showing lengthening of auricular systole during compression of the right vagus (Figs. 5 and 6). The most notable examples are the summits *P 3* and *P 4*

in Fig. 6, which are 0·245 and 0·280 sec. respectively as compared with *P 8* (0·105 sec.) after the compression was withdrawn. None of my records of left vagus compression reveal any prolongation of auricular systole. I have not observed any shortening of auricular systole after the injection of atropin. Thus all the available evidence demonstrates that the vagus has less influence on the conductivity of the auricles than on their rate or contractility.

V. *Tonicity.* The difficulty in determining the degree and variation of tonicity in the human heart is fully recognized. The tone of the cardiac muscle cannot be ascertained with any approach to accuracy by any of the ordinary methods of clinical examination, nor even by the more precise methods of orthoröntgenography and teleröntgenography. Such methods of examination reveal to us, among other facts, the size of the heart; and certain deductions regarding the degree of dilatation may be drawn from an analysis of the patient's symptoms and of the results furnished by physical examination. Enlargement, dilatation, increased intra-cardiac pressure and inefficiency of the heart may be associated with depression of tone in the heart muscle, but it does not follow that they are due to that depression, for as pointed out by Gaskell (26) increased relaxation of the muscle does not necessarily imply depression of tone.

According to Gaskell (26), the muscular tissue of the heart relaxes when the vagus is stimulated. Luciani (44) states that 'the greater diastolic relaxation produced by the vagus is not necessarily associated with diminished frequency and height of systole. . . This fact has been substantially confirmed for mammalia by the researches of MacWilliam, Johannson and Tigerstedt, François-Franck, and especially by Stefani.' Again, it will be remembered that Roy and Adami (63) demonstrated that vagus stimulation, and likewise arrest of respiration, produce dilatation both of auricles and ventricles in the mammalian heart, with progressive increase of the residual blood due to progressive weakening of the heart walls; but these observers expressly state that the increased diastolic volume of the ventricles is due to increased intra-ventricular pressure during diastole and not to any alteration of tonicity in the relaxed walls of the heart.

Gaskell (26), however, maintained that the tonicity of the heart muscle is depressed by vagus stimulation. His classical experiments (24) on the quiescent auricle of the tortoise demonstrate 'the positive electrical variation in consequence of vagus stimulation, and also that such electrical change takes place so slowly that its course can easily be registered by an observer who is noting the position of the galvanometer needle only every five seconds. Such a rate of change is remarkably different from the rapid movement in the opposite direction, which occurs when a contraction takes place.' Gaskell (26) further states that in the frog and toad 'the augmentor nerve causes an electrical change in the muscular tissue of the opposite kind to that caused by the inhibitory nerve, and it is worthy of note that the process to which this increase of negativity is due is, like the corresponding positive change, a slow slight one, very different indeed from the rapid excessive process which initiates a contraction. The contrast between this slow motor effect of the augmentor nerve and the rapid movement

of the galvanometer needle in the same direction when a contraction takes place is most striking. The nature of the electrical change in the case of both nerves seems to me to point to the conclusion that the change which occurs in the quiescent muscle, upon stimulation of the inhibitory nerve, is of the nature of a relaxation or diminution of tone, while the change which occurs upon stimulation of the augmentor nerve is of the nature of an increase of tone.' These slow variations of potential were not observed by Gotch (29), but Burdon-Sanderson (3) and Fano and Fayod (19) admitted that the results of their own experiments were in harmony with those of Gaskell. In a more recent communication, however, Fano (18) refers to the vagus as having a positive tonotropic effect, and Bottazzi (2) expresses the same belief. In Einthoven's (15) recent researches on the effects of vagus stimulation in the dog no slow positive variation was observed, nor is it seen in the records published by Rothberger and Winterberg (61, 62), but those of Meek and Eyster (80) show it clearly.

In the course of my observations with the string-galvanometer I have repeatedly observed slow, shallow oscillations on the electro-cardiographic record (Fig. 13). These oscillations, which are of slower rate than the respiratory movements, indicate slow differences of potential between the two limbs of the patient. These oscillations are not caused by variations in the strength of the magnetic field, nor by voluntary movements of the patient, but may perhaps represent slow contractions of the musculature of some of the abdominal viscera such as the stomach or spleen. It is also possible that the oscillations may be due to periodic variations in the tone of the cardiac musculature, comparable to the oscillations or tone-waves described by Fano (17), Bottazzi (2), Howell (36), and Porter (56).

In some electro-cardiographic records of vagus compression I have observed a difference of potential somewhat similar to that recorded by Gaskell in the quiescent auricle of the tortoise during vagus stimulation. In these electrocardiograms there is a gradual and progressive difference of potential during and after the compression period (Figs. 4, 8, 9, 13, and 14). In some instances the fall of the curve is preceded by a comparatively short initial rise (Fig. 1). The difference of potential may be so slow that unless the photographic plate be travelling at a slow speed only a portion of the descending curve may be registered (Fig. 2). On a slowly moving plate, however, the change of potential is represented by a curve (Fig. 14) falling slowly and progressively for about 10–15 sec., and thereafter rising still more gradually towards the original level. In some persons the slow difference of potential may ensue upon a right vagus compression which fails to retard the auricles or to weaken the force of their beats. In other individuals this difference of potential may accompany and follow a compression of the right vagus, which retards and weakens the auricles, whereas in the same patient the difference of potential is absent or very slight on compression of the left vagus, which is not associated with any notable chronotropic or inotropic effects.

Is this slow difference of potential ensuing on vagus compression in man of

the same nature as that described in the quiescent auricle of the tortoise by Gaskell? It cannot be ascribed to mere contact of the compressing finger with the patient, for the finger, whether or not it be insulated, may be laid upon the patient's neck, face, or arm without any consequent alteration in the position of the string. Arrest of respiration, forcible respiratory movements, elevation of the head from the couch, and movements of those limbs that are not immersed in the baths do not cause this form of curve. But if a record is being taken by D. II (right hand and left foot), a similar slow change of potential may be recorded when the patient slowly contracts and then relaxes the muscles of his right upper or left lower limb. This fact suggests that the slow difference of potential represented by a curve such as that in Fig. 14 may be due not to any vagus effect on the heart or other viscus, but to involuntary tonic contraction of muscles in the right arm or left leg of the patient. In anaesthetized dogs vagus stimulation may cause marked inhibitory effects on the heart without any slow difference of potential being recorded (Einthoven (15), Rothberger and Winterberg (61, 62)), whereas my observations have been made on patients. They were reclining quietly on the insulated couch, and apparently they did not move; but the possibility of some muscles in the arm or leg having contracted cannot be excluded with certainty. The subject is being investigated further by Dr. G. D. Mathewson in this laboratory.

VI. *Fibrillation of the auricles.* (1) *Compression of vagus.* According to Winterberg (79), Hirschfelder (35), Hering (30), Rothberger and Winterberg (61), and Lewis and Schleiter (42), auricular fibrillation ensues in consequence of increased excitability of multiple foci in the auricles. The main arguments on which this hypothesis is based are (1) the nature of the auricular response to faradic stimulation of varying intensity. Weak stimulation causes single auricular extra-systoles; strong stimulation causes a series of rapid rhythmic auricular beats; more intense stimulation causes fibrillar contraction of the auricular musculature. (2) Supra-ventricular extra-systoles may be the forerunners of auricular fibrillation. I have records of several cases illustrating this sequel of events. (3) Rhythmic auricular tachycardia and paroxysms of auricular fibrillation may occur in the same individual (Mackenzie (45), Turnbull (68), Lewis and Schleiter (42)). (4) Microscopic examination in cases of auricular fibrillation often reveals evidence of a subacute inflammatory reaction in many parts of the auricular walls. There is therefore considerable evidence in support of the theory that increased excitability of multiple foci in the auricles is a factor in the production of auricular fibrillation in the human subject; but I doubt whether it is the sole factor. The effects of vagus compression and of atropin suggest that depression of conductivity in the auricles plays a not unimportant part in the production of fibrillation in man. The chief arguments on which I base this opinion are (1) as the auricular muscle fibres contract frequently and in an inco-ordinate manner, the transmitted stimuli are rapid, weak, and of varying intensity. Auricular conductivity will vary according to the rate and strength of the stimuli. Those stimuli that are

weakest will be blocked soonest, those that are strongest will travel furthest.[1] (2) If auricular fibrillation were due solely to increased excitability, both vagus stimulation, whether mechanical or faradic, and drugs that stimulate the activity of the vagus ought to check, or even arrest, fibrillar contraction, and atropin ought to promote it. Both Fischel (20) and Philips (55) concluded that vagus excitation may arrest auricular fibrillation, but the more recent researches of Winterberg (78, 79) demonstrate clearly that vagus stimulation of moderate intensity favours the onset of fibrillation. Winterberg (78) also showed that in a heart under the influence of atropin, fibrillation ceases coincidently with cessation of faradic stimulation, whereas in a heart without atropin the fibrillation persists as an after-effect (Nachflimmern). Acting on Mackenzie's (45) advice I have found that under the influence of digitalis an auricular flutter may pass into fibrillation. But in no case under my own observation could I ascribe the onset of auricular fibrillation to compression of the vagus, and in no instance have I observed auricular fibrillation to be checked or arrested by vagus compression. The succession of small, frequent, irregular deflexions persisted throughout the electro-cardiograms recorded before, during, and after compression of the vagus. (3) In the auricular walls from cases of auricular fibrillation I have found microscopic evidence not merely of lymphocytic infiltration, but also of diffuse increase of fibrous tissue, similar to that recorded by Radasewsky (57), and Dehio (13), and corresponding to the peri-fascicular fibrosis described by Cowan (6). This diffuse fibrosis must tend to impair the conduction of stimuli, and especially of weak stimuli, throughout the auricular wall, whether this be effected by nervous, muscular, or neuro-muscular pathways; and any factor, such as vagus stimulation, which can depress conductivity in the auricles still further may thus cause blockings in their walls whereby inco-ordinate contraction of the irritable muscle fibres may ensue.

(2) *Atropin.* From the foregoing argument it will be evident that any influence depressing the excitability of the auricular muscle or improving the conductivity of the auricular tissues ought to check fibrillation and promote co-ordinate contraction of the muscle fibres. I have already (p. 53) mentioned one instance in which atropin appeared to depress the excitability of an unduly irritable focus in the auricle, and the influence of atropin in improving conductivity may be regarded as established. It is doubtful, however, whether this drug can be of service in most cases of auricular fibrillation. Any beneficial effects atropin may exert on the auricles must be more than counteracted by the coincident improvement in the propagation of stimuli to the ventricles, which will therefore beat at a faster rate. The only cases of auricular fibrillation in which atropin might be used beneficially would be those in which the ventricular rate, as described by Mackenzie, is unduly retarded.

VII. *Auricular flutter and paroxysmal tachycardia.* In the patient presenting the condition which has been called auricular flutter by Jolly and

[1] In the case of the ventricle, the same observations were advanced by Gaskell (27) to explain fibrillar contraction.

myself (37) bilateral compression of the vagus and atropin have invariably failed to influence the auricles, which have continued to beat rhythmically at a rate of 250–300 per minute. The same negative results of atropin in cases of auricular tachycardia are recorded by Hertz and Goodhart (34), and by Rihl (59); and in Rihl's cases the auricular rate was uninfluenced by vagus compression. In one case of paroxysmal tachycardia, in which the ventricles were proved to be contracting rhythmically at a rate of 160–220 per minute, firm bilateral compression was applied to the vagi, but the tracings revealed no retardation of the heart. A few days later, when the heart was beating rhythmically about seventy-five times per minute, neither right nor left vagus compression retarded the heart's rate. This was true in two recent cases of auricular flutter.

Effects on the Auriculo-ventricular Bundle System.

I. *Conductivity.* (1) *Compression of vagus.* It is well known that in animals the rate of conduction of stimuli from auricle to ventricle may be depressed by vagus stimulation (Gaskell (23), MacWilliam (51), Roy and Adami (63), Muskens (54)), by heleborein (Knoll (39)), by digitalis (Cushny (8), von Tabora (64)), and by asphyxia (Mathison (52)). Depression of auriculo-ventricular conductivity in the human heart has been recorded after digitalis (Mackenzie (48), Cushny (9), &c.), strophanthus, and squill (Turnbull (69)), after swallowing (Mackenzie (49)), and during compression of the vagus (Thayer and Peabody (66), and Robinson and Draper (60)).

I find that compression of the vagus, either on the right or left side of the neck, does not usually cause any depression of conductivity in the auriculo-ventricular bundle system. The rate of the whole heart may be retarded, and the force of the auricular beats may be weakened by right vagus compression without any associated lengthening of the *As–Vs* interval (Figs. 1 and 2). The first *As–Vs* interval after a standstill of the whole heart (Fig. 8) may be of normal duration. Left vagus compression may weaken the auricular beats without lengthening the *As–Vs* interval (Fig. 10). But in rare instances compression of the right vagus may depress the conductivity of the auriculo-ventricular bundle system. Thus in Fig. 5 the *P–R* interval before compression of the right vagus was 0·17 sec., whereas the fourth *P–R* interval after the commencement of compression is 0·24 sec. In Fig. 6, from the same patient, the depression of conductivity is still greater, for while the first *P–R* interval after the commencement of compression is 0·31 sec., the next auricular systole, *P 4*, which lasts 0·28 sec., is not followed by a ventricular beat until 1·43 sec. has elapsed. This ventricular beat may be in response to *P 4*, and the succeeding ventricular beat may be the response to *P 6*, or alternatively no effective stimulus is conducted to the ventricles during the long period elapsing between *P 3* and *P 7*, and *R 4* and *R 5* are the initial deflexions of idio-ventricular beats. Accepting either of these explanations, we must conclude that the vagus compression was associated with a transient auriculo-ventricular heart-block, for the fifth auricular systole, *P 5*, is not followed

by a ventricular response. As this auricular systole occurs at a time when the ventricles are in systole, the auricles cannot expel their contained blood, and consequently the succeeding auricular contraction, *P 6*, is premature. The question of synchronous contraction of auricle and ventricle causing prematurity of the succeeding auricular beat has been discussed fully by Cowan and myself (7) in a former paper. An electro-cardiogram demonstrating a similar sequence of events in a female patient suffering from mitral stenosis and incompetence is shown in Fig. 7. Here each ventricular extra-systole occurs at the same time as a physiological beat of the auricles, and is followed by a second premature beat in which both auricles and ventricles are premature, the auricular contraction preceding the ventricular and being represented by an inverted *P* deflexion.

The onset of a continuous coupled rhythm of the ventricles in cases of auricular fibrillation after the prolonged administration of digitalis was formerly ascribed to the drug depressing the conductivity of the auriculo-ventricular bundle, and thereby shielding the ventricles from the rapid, irregular, auricular impulses. But it is now known that in this form of coupled rhythm the second beat of each couple originates in the ventricles and yields an atypical electro-cardiogram. I have found that although in some cases of auricular fibrillation vagus compression may cause slowing of the ventricles, in others vagus compression may fail to lessen the frequency of the disorderly ventricular beats and yet digitalis subsequently induces well-marked retardation. Moreover, I find that vagus compression seldom produces any coupling of the ventricular beats in cases of auricular fibrillation. The contrast in this respect between vagus compression and digitalis is striking. It is therefore permissible to infer that the well-known effect of digitalis in causing a coupled rhythm in auricular fibrillation is not due solely to the drug depressing conductivity in the auriculo-ventricular bundle.

(2) *Atropin.* In the dog, the propagation of stimuli to the ventricles is accelerated by section of the vagi (Einthoven, 15), and administration of atropin may lessen or abolish depression of conductivity in the human auriculo-ventricular bundle (Gibson and Ritchie (28), Wardrop Griffith (71), Volhard (70), &c.). This effect of atropin is so well established that I need not dwell upon it further than by referring to one test in a case of digitalis heart-block. In this case (Fig. 24) the injection of 0·03 grain of atropin sulphate lengthened the *a–c* interval from 0·20 to 0·32 sec. for a period of seven minutes. Thereafter the *a–c* interval shortened until it was only 0·15 sec. at the sixteenth minute, and from the sixteenth until the thirty-eighth minute the *a–c* interval remained between 0·15 and 0·18 sec. A comparison of the two curves in Fig. 24 shows that before atropin improves conductivity in the auriculo-ventricular bundle there may be an initial and shorter phase of depression of conductivity, which persists for the same length of time as the initial retardation of auricular rate.

II. *Excitability.* Although it is probable that many supra-ventricular extra-systoles may originate in the nodal tissue of the auricles, and that many ventricular extra-systoles originate in the terminal ramifications of the auriculo-

ventricular bundle, the precise localization of the unduly irritable foci is still largely a matter of speculation. The effects of vagus compression and of atropin on the production or abolition of extra-systoles are therefore discussed under the headings of auricles (p. 53) and ventricles (p. 63) respectively.

Effects on the Ventricles.

Gaskell (26) stated that the vagus has no influence whatever on the ventricle of any cold-blooded vertebrate except the Amphibia. But in the mammalian heart, as MacWilliam (51) has shown, vagus stimulation may cause ventricular standstill either by inhibition or depression of the inherent rhythmic property (stimulus production) of the ventricles, or by the absence of the incitations to contraction normally communicated to them. MacWilliam has also demonstrated that vagus stimulation may markedly depress the strength, and prolong the duration, of the ventricular beats; but that if excitability be depressed at all the change is a very slight one and not at all comparable to the depression of auricular excitability.

In describing the effects of vagus stimulation and of atropin on the human ventricles, it is convenient to consider the results (I) in complete auriculo-ventricular heart-block, (II) in partial heart-block, and (III) in hearts with a wholly physiological rhythm and with good conductivity in the bundle system.

I. *In complete auriculo-ventricular dissociation.* Bilateral vagus compression was applied repeatedly in one case, and unilateral compression in a second, but the ventricles were never influenced. The duration of ventricular systole and diastole remained unaltered, the beats were all rhythmic and uniformly strong. In the case recorded by Jolly and myself (37), and in two other cases (Fig. 23), atropin did not influence the rate, rhythm, or strength of the ventricular beats. The same uniformly negative results after administration of atropin have been recorded in many cases of complete auriculo-ventricular dissociation.

II. *In partial heart-block.* In these cases the well-known effects of vagus stimulation and of atropin upon the rate, rhythm, and strength of the ventricular beats are usually the indirect effects either of changes in rate or strength of the auricular beats, or of altered conductivity in the bundle system. A transient heart-block due to compression of the right vagus is shown in Fig. 6, and a curve depicting a similar event as an initial effect of atropin is shown in Fig. 24.

III. *In hearts with a wholly physiological rhythm and good conductivity in the bundle system.* (i) *Rate.* During vagus compression and after atropin the ventricular rate is in nearly all instances the same as the auricular, whether the latter be unchanged, retarded, or accelerated. Ventricular retardation, like the auricular, ensues gradually and passes off gradually, but in some instances the auricles escape from vagus inhibition before the ventricles (Figs. 6, 9, and 19), as occurs in the dog (Einthoven, 15). After prolonged standstill of the whole heart the ventricles may respond to the first auricular contraction (Fig. 8), or the auricles may beat twice before the ventricles respond (Figs. 9 and 19). In other instances with marked retardation, the ventricular rate and rhythm

may perhaps differ from the auricular (Fig. 6) owing to the occurrence of idio-ventricular contractions, as discussed on p. 60.

(ii) *Excitability.* I have failed to obtain conclusive evidence of depression of ventricular excitability during compression either of right or left vagus. In several cases, presenting numerous ventricular extra-systoles, vagus compression did not tend to diminish their frequency, and in one case of coupled rhythm due to a ventricular extra-systole recurring after each physiological beat neither right nor left vagus compression abolished the coupled rhythm. Again, I have not observed any indication that vagus compression has any primary positive bathmotropic effect on the ventricles. In only one electro-cardiogram, from a case of auricular fibrillation, have I seen a ventricular extra-systole occur for the first time during the period of compression.

There is some evidence, however, that atropin can cause ventricular extra-systoles to disappear for a time. In cases of auricular fibrillation, for example, the drug can abolish the continuous coupled rhythm of the ventricles which is induced by drugs of the digitalis group, and in which the second beat of each couple is a premature ventricular beat yielding an atypical electro-cardiogram. This effect is shown in the diagram (Fig. 26) representing the ventricular rate per minute before and after two injections of atropin sulphate. The coupled rhythm disappeared suddenly eight and a half minutes after the first injection, and reappeared from the tenth until the twelfth minute. But from then onwards until the end of the record there was a 'single' rhythm, except for a brief recurrence of the coupled beats between the eighteenth and nineteenth minutes. The diagram shows that the cessation of the ventricular extra-systoles cannot be ascribed to acceleration of the ventricular rate, because this was constantly retarded after the injections.

In another patient, a woman aged 30, suffering from mitral incompetence and presenting a continual coupled rhythm in which a ventricular extra-systole recurred after each physiological beat of the heart, atropin effected a transient abolition of the extra-systoles on two separate occasions. In this case compression of the right vagus had previously been tried nine times, and that of the left vagus five times, without any effect on the rate or rhythm of the heart. Records of the first atropin test were taken by means of the Knoll-Hering polygraph and showed that the rate of the coupled ventricular beats was 83·3 per minute before the injection of 0·02 grain atropin sulphate, and that the coupled rhythm persisted with a ventricular rate varying from 77·9 to 108·1 per minute until between the seventeenth and eighteenth minutes the coupled rhythm disappeared suddenly. The rate was then 88·2 per minute. The extra-systoles had not recurred when the record closed at the 42nd minute, the ventricular rate being then 101·6 per minute. On the following day the coupled rhythm had returned; 0·02 grain of atropin sulphate was again given subcutaneously, and a series of records were obtained by means of the string galvanometer. Prior to the injection, the heart's rate was 73·2 per minute. The coupled rhythm persisted for 28 minutes after the injection, but from the

28th until the 48th minute, when the record ceased, only occasional ventricular extra-systoles occurred. It may be argued that the acceleration of the heart brought about the disappearance of the extra-systoles. A comparison of two records (Figs. 11 and 12) demonstrates that at the 20th minute (Fig. 11) the coupled rhythm persisted with an auricular rate of 97·9 per minute, whereas only an occasional ventricular extra-systole occurred at the 48th minute (Fig. 12) when the rate was 100·8 per minute. This slight difference of rate can hardly be regarded as the only factor in abolishing the coupled rhythm, and its cessation may possibly have been due to the atropin depressing the excitability of an unduly irritable focus in the ventricles. In another case, a man aged 29, with an almost constant coupled rhythm due to a ventricular extra-systole recurring after each physiological beat, the power of atropin to abolish extra-systoles was not so manifest, although the same dose, 0·02 grain, was administered. Seven electro-cardiograms, each representing a period of six seconds, were taken. There were three extra-systoles in the first record, three minutes before atropin; one in the second, ten minutes after atropin; two in the third, seven minutes later; and four in the fourth, three minutes later. A continual coupled rhythm, with six extra-systoles, was present in each of the records taken between the 25th and the 36th minute after atropin.

(iii) *Contractility.* (1) *Compression of vagus.* Vagus stimulation, as demonstrated by MacWilliam (51), may depress the contractility of the ventricular muscle in the mammalian heart, but Roy and Adami (63) maintain that the less complete systolic shortening of the ventricular fibres is not due to any weakening of the ventricular contraction, but is due entirely to the more distended condition of the ventricles and increased contraction volume. I have found that vagus compression causing a moderate degree of ventricular retardation is in most instances associated either with no change or with slight increase of strength of the ventricular beats. The increase is usually proportionate to the lengthening of the antecedent diastole, and may therefore be regarded as a secondary positive inotropic effect. The difference that is noticeable between the strong ventricular beats and the weakened auricular beats (Figs. 1 and 10) is striking. I have not observed the deflexion *T* becoming flattened or inverted during vagus compression in man, as is described in the dog by Einthoven (15); but other evidence of marked negative inotropic effect on the ventricles may be observed.

In some instances the amplitude of the arterial pulse-beats may be diminished during compression either of the right or left vagus, even in the absence of retardation. Thus in Fig. 21, obtained from a girl aged 17, suffering from acute rheumatism and mitral incompetence, the force of successive pulse-beats becomes reduced during the period of right vagus compression, while the rate remains practically constant. The negative inotropic effect passes off while compression is still being maintained. In this patient compression of the left vagus produced the same effect.

After ventricular standstill for several seconds, the first ventricular contrac-

tion and those succeeding it are often of good strength (Figs. 8, 17), as is the case in the dog. In this respect the contrast between the auricles and the ventricles is remarkable. For example, in the case of a railway servant aged 53, suffering from cerebellar tumour, the first pulse-beat after standstill for three seconds is stronger than those preceding the standstill (Fig. 17); and in a miner aged 46, affected with chronic gastric catarrh, the first ventricular deflexions recorded in an electro-cardiogram (Fig. 8) after ventricular standstill for four seconds are as large as those preceding the standstill. In the cerebellar tumour case, however, the pulse-beats after ventricular standstill for seven or more seconds show an ascending staircase (Figs. 18 and 19) similar to those recorded by Webster (74) and Laslett (40). In Fig. 18 the last beat before the standstill is of slightly lesser amplitude than those preceding it. I have no other record of this phenomenon.

(2) *Atropin.* The effect of atropin on the strength of the ventricular contractions depends mainly, if not wholly, on the degree of acceleration. If the drug does cause any primary positive inotropic effect it is masked by the secondary negative inotropic effect resulting from the acceleration.

(iv) *Conductivity.* The rate of conduction of stimuli through the human ventricle cannot be determined in the same manner as in the exposed heart of one of the lower animals. Although the duration of ventricular systole may be influenced by the degree of blood-pressure in the aorta as well as by other factors, it is possible that in some instances prolongation of ventricular systole may be an indication of depression of intra-ventricular conductivity. In my observations I have found that the duration of ventricular systole almost constantly remains unchanged by vagus compression, even although the rate is notably decreased (Figs. 1, 2, 4). The record in Fig. 6 is the only one I have yet obtained revealing definite evidence of lengthened ventricular systole. Here the ventricular beat following *P 3* lasts 0·45 sec. as compared with that following *P 2* (0·35 sec.), an increase of 30 per cent. The shortening of ventricular systole under the influence of atropin is either very slight or wholly inappreciable.

After-effects of Vagus Compression.

The mode of escape of the human auricles from vagus inhibition has been described in the sections of this paper dealing with the auricles. It has been shown that the auricles usually begin to escape from vagus inhibition during the period of compression, as demonstrated by the increasing rate and strength of the auricular beats (Fig. 4); and auricular standstill usually, if not invariably, terminates before the compression is withdrawn (Figs. 8 and 19). The inhibitory effects on the auricles usually pass off gradually, successive auricular beats becoming quicker and stronger. The rate of recovery in the auricles varies widely in different tests, but as a rule is proportionate to the degree of antecedent inhibition. The rate of recovery in the auriculo-ventricular bundle is usually more rapid than that in the auricles.

The mode of ventricular escape from vagus inhibition is not constant. In some instances (Figs. 6, 9, 19) the ventricular standstill persists longer than the auricular, either because of depressed conductivity in the auriculo-ventricular bundle or because the inhibitory influence on the ventricles themselves predominates over that on the auricles. In a few instances (Fig. 6) it is possible that the first ventricular beats after prolonged ventricular standstill may be idio-ventricular.

I have not observed either the auricular or ventricular beats to be augmented in strength during the period of escape. If the retardation of the whole heart induced by vagus compression is ever followed by acceleration, the increase of rate is very slight. This observation is in harmony with that recorded by Tigerstedt (67).

In two cases I have observed an extra-systole appearing during the period of escape. One patient was a woman, aged 25, suffering from diabetes mellitus. She had previously presented numerous extra-systoles, but on the day when the test was performed a long tracing was taken by means of the ink-polygraph, and the only extra-systole that was recorded was one occurring about three seconds after withdrawal of pressure from the right vagus (Fig. 22). In the second case, a woman aged 45 affected with mitral disease, the extra-systole occurring about five seconds after release of pressure from the right vagus was the only one that was recorded (Fig. 16). Both in Figs. 16 and 22 the post-extrasystolic pause is not fully compensatory. This suggests that the extra-systoles were of supra-ventricular origin, and that they are comparable to the extra-systoles recorded by Weiland (75), and commented upon by Hering (33) as occurring in rabbits after cessation of weak vagus stimulation. We know that stimulation of the accelerator nerve undoubtedly promotes the onset of extra-systoles (Rothberger and Winterberg (61, 62)), that the vagus contains accelerator as well as inhibitory fibres, and that the latent period of accelerator stimulation is longer than that of inhibition; and consequently the delayed onset of extra-systoles after compression of the vagus suggests that they may represent an accelerator effect.

The occurrence of extra-systoles in the human heart after compression of the vagus, although not necessarily of much significance, may reveal an alternation in the pulse-beats succeeding the extra-systole (Fig. 16), even although alternation had been wholly latent hitherto. The grave prognostic significance of the pulsus alternans is admitted, and as compression of the right vagus can reveal latent alternation, the test may be of value in prognosis. The patient from whom the record in Fig. 16 was obtained died about a month later after a short attack of auricular fibrillation. The administration of atropin may likewise reveal latent alternation. For example, in a man aged 76 affected with arterial sclerosis, alternation had not been observed until the pulse-rate quickened to 102·5 per minute after an injection of 0·025 grain atropin sulphate (Fig. 25). No record of the auricular beat was being taken, so I am unable to say whether the alternation was induced by simultaneous contraction of auricle and ventricle,

as in the case described by Wardrop Griffith (72). But the point that I desire to emphasize is that atropin, when it causes alternation, may reveal inefficiency of the heart, for alternation is not observed when a healthy heart is beating 102 times per minute.

Summary.

The action of the vagi on the human heart is closely comparable to that of the vagi on the heart of other mammals. Compression of the right vagus may depress the rate and strength of the auricular beats, may prolong auricular systole, and may depress the conductivity of the auriculo-ventricular bundle system. The inhibitory effects of the vagus on the human auricles ensue gradually, and usually pass off gradually while the compression is still being maintained. Compression of the right vagus has not depressed the excitability of the human auricular muscle when in fibrillar contraction or in flutter. Depression of conductivity is probably an important factor in the production of fibrillation in the human heart.

In three cases of complete auriculo-ventricular dissociation the vagi had no apparent influence on the ventricles. In hearts with a normal rhythm and good conductivity in the auriculo-ventricular bundle system, vagus compression may depress the rate and contractility of the ventricles, and less frequently may prolong the duration of ventricular systole. The depression of ventricular rate is usually proportionate to the degree of auricular retardation.

In some instances the auricles escape from vagus inhibition before the ventricles; in others ventricular standstill may perhaps terminate by the occurrence of idio-ventricular contractions. Extra-systoles may occur during the escape of the heart from vagus inhibition.

The inhibitory effects of left vagus compression are as a rule less effective than those of right vagus compression, and the latter are almost uniformly the reverse of those induced by atropin.

REFERENCES.

1. Bayliss and Starling, *Journ. of Physiol.*, Camb., 1892, xiii. 407.
2. Bottazzi, *Arch. ital. de biol.*, Turin, 1901, xxxvi. 277.
3. Burdon Sanderson, *Journ. of Physiol.*, Camb., 1887, viii, Proc. 27.
4. Cardarelli, *Arch. ital. de biol.*, Turin, 1891, xiv. 205.
5. Cohn, *Journ. of Exp. Med.*, N. York, 1912, xv. 49.
6. Cowan, *Journ. of Pathol. and Bacteriol.*, Edinb. and Lond., 1904, ix. 209.
7. Cowan and Ritchie, *Quart. Journ. of Med.*, Oxford, 1910–11, iv. 55.
8. Cushny, *Journ. of Exp. Med.*, N. York, 1897, ii. 233.
9. Cushny, *American Journ. Med. Sci.*, 1911, N.S., cxli. 469.
10. Czermak, *Gesammelte Schriften*, Leipz., 1879, i. 2. 779.
11. Czermak, *Ibid.*, 788.
12. Danielopolu, *Comptes rend. Soc. de Biol.*, Paris, 1908, lxiv. 969.
13. Dehio, *Deutsch. Arch. f. klin. Med.*, 1899, lxii. 1.
14. Dixon, *Manual of Pharmacology*, 3rd edition, Lond., 1912, 79.
15. Einthoven, *Arch. f. d. ges. Physiol.*, Bonn, 1908, cxxii. 517.

16. Engelmann, *Arch. f. Anat. u. Physiol.*, Leipz. (Physiol. Abt.), 1902, 103.
17. Fano, *Beiträge z. Physiologie, Carl Ludwig gewidmet*, Leipz., 1887, 287; *Arch. ital. de biol.*, Turin, 1888, ix. 61.
18. Fano, *Archivio di fisiol.*, Firenze, 1904, i. 249.
19. Fano and Fayod, *Arch. ital. de biol.*, Turin, 1888, ix. 143.
20. Fischel, *Arch. f. exp. Pathol. u. Pharmak.*, Leipz., 1897, xxxviii. 228.
21. Flack, *Journ. of Physiol.*, Camb., 1910–11, xli. 64.
22. Garrey, *Amer. Journ. of Physiol.*, 1911, xxviii. 330.
23. Gaskell, *Journ. of Physiol.*, Camb., 1883, iv. 43.
24. Gaskell, *Ibid.*, 1887, viii. 404.
25. Gaskell, *Philos. Trans. Royal Soc.*, Lond., 1882, clxxiii. 3. 993.
26. Gaskell, *Schäfer's Text-book of Physiology*, Edinb. and Lond., 1900, ii. 203–21.
27. Gaskell, *Ibid.*, 192.
28. Gibson and Ritchie, *Practitioner*, Lond., 1907, lxxviii. 589.
29. Gotch, *Journ. of Physiol.*, Camb., 1887, viii, Proc. 26.
30. Hering, *Verhandl. d. deutsch. pathol. Gesell.*, Jena, 1910, xiv. 49.
31. Hering, *Arch. f. d. ges. Physiol.*, Bonn, 1905, cviii. 281.
32. Hering, *Ibid.*, 1909, cxxvii. 155.
33. Hering, *Zeitschr. f. exp. Pathol. u. Therap.*, 1911, ix. 491.
34. Hertz and Goodhart, *Quart. Journ. of Med.*, Oxford, 1908–9, ii. 213.
35. Hirschfelder, *Bull. Johns Hopkins Hosp.*, Balt., 1908, xix. 322.
36. Howell, *Text-book of Physiology*, Philad. and Lond., 2nd edit., 1907, 530.
37. Jolly and Ritchie, *Heart*, Lond., 1910–11, ii. 177.
38. Kahn, *Arch. f. d. ges. Physiol.*, Bonn, 1911, cxl. 627.
39. Knoll, *Sitzungsb. d. k. Akad. d. Wiss. in Wien*, 1894, ciii, Abt. III (math.-naturw. Classe), 298.
40. Laslett, *Quart. Journ. of Med.*, Oxford, 1908–9, ii. 347.
41. Lewis, *Heart*, Lond., 1910–11, ii. 23.
42. Lewis and Schleiter, *Ibid.*, 1912, iii. 173.
43. Luciani, *Human Physiology*, English transl., Lond., 1911, i. 323.
44. Luciani, *Ibid.*, 326.
45. Mackenzie, *Heart*, Lond., 1910–11, ii. (Case 37) 378.
46. Mackenzie, *Ibid.*, 1910–11, ii. 289.
47. Mackenzie, *Ibid.*, 1909–10, i. 23.
48. Mackenzie, *Ibid.*, 1910–11, ii. 292.
49. Mackenzie, *Brit. Med. Journ.*, 1906, ii. 1109.
50. MacWilliam, *Journ. of Physiol.*, Camb., 1885, vi. 226.
51. MacWilliam, *Ibid.*, 1888, ix. 345.
52. Mathison, *Heart*, Lond., 1910–11, ii. 54.
53. Meyer, *Das Hemmungsnervensystem des Herzens*, Berlin, 1869.
54. Muskens, *Amer. Journ. of Physiol.*, 1898, i. 486.
55. Philips, *Arch. internat. de Physiol.*, Liège et Paris, 1904–5, ii. 271.
56. Porter, *Amer. Journ. of Physiol.*, 1905–6, xv. 1.
57. Radasewsky, *Zeitschr. f. klin. Med.*, Berlin, 1895, xxvii. 381.
58. Rihl, *Arch. f. d. ges. Physiol.*, Bonn, 1906, cxiv. 545.
59. Rihl, *Zeitschr. f. exp. Pathol. u. Therap.*, Berlin, 1911, ix. 277.
60. Robinson and Draper, *Journ. of Exp. Med.*, N. York, 1911, xiv. 217; 1912, xv. 14.
61. Rothberger and Winterberg, *Arch. f. d. ges. Physiol.*, Bonn, 1911, cxli. 343.
62. Rothberger and Winterberg, *Ibid.*, 1911, cxlii. 461.
63. Roy and Adami, *Philos. Trans. Roy. Soc. Lond.*, B, 1892, clxxxiii. 199.
64. von Tabora, *Zeitschr. f. exp. Pathol. u. Therap.*, Berlin, 1906, iii. 499.
65. Thanhoffer, *Centralbl. f. d. med. Wiss.*, Berlin, 1875, xiii. 403.
66. Thayer and Peabody, *Arch. of Int. Med.*, 1911, vii. 289.
67. Tigerstedt, *Lehrbuch d. Physiol. d. Kreislaufes*, Leipz., 1893, 271.
68. Turnbull, *Heart*, Lond., 1911, iii. 89.
69. Turnbull, *Ibid.*, 1910–11, ii. 15.

70. Volhard, *Deutsch. Arch. f. klin. Med.*, 1909, xcvii. 348.
71. Wardrop Griffith, *Quart. Journ. of Med.*, Oxford, 1909–10, iii. 126.
72. Wardrop Griffith, *Heart*, Lond., 1912, iii. 143.
73. Wasilewsky (quoted by Dogiel), *Arch. f. d. ges. Physiol.*, Bonn, 1911, cxlii. 109.
74. Webster, *Glasgow Hosp. Reports*, 1901, iii. 413.
75. Weiland, *Zeitschr. f. exp. Pathol. u. Therap.*, Berlin, 1911, ix. 486.
76. Wenckebach, *Arch. f. Anat. u. Physiol.*, Leipz. (Physiol. Abt.), 1908, Suppl.-Bd. 53.
77. Wesley Mills, *Journ. of Physiol.*, Camb., 1885, vi. 246.
78. Winterberg, *Arch. f. d. ges. Physiol.*, Bonn, 1907, cxvii. 223; 1908, cxxii. 361.
79. Winterberg, *Ibid.*, 1907, cxvii. 223; *Zeitschr. f. exp. Pathol. u. Therap.*, 1906, iii. 182.
80. Meek and Eyster, *Amer. Journ. of Physiol.*, 1912, xxx. 271.

DESCRIPTION OF FIGURES.

In each electro-cardiographic record the tension of the string was adjusted so that, with a magnification of 450 diameters, a difference of potential of 1 millivolt introduced into the circuit containing the galvanometer and patient gave a deflexion of 1 cm.

In all the electro-cardiograms, which are by derivation II (right hand and left foot), the period of vagus compression is indicated by the electric signal. In Figs. 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, and 12, the tuning-fork record is 28·57 per second. In Figs. 9, 13, and 14, the time-marker indicates 0·5 sec.; in Figs. 15, 16, 17, 18, 19, 20, 21, and 22, the time-marker records 0·2 sec.

PLATE 1, FIG. 1. Compression of the right vagus slows the whole heart, and depresses auricular contractility. The escape from vagus inhibition begins before the compression is withdrawn. During and after the compression there is a slow difference of potential.

FIG. 2. Compression of the right vagus causes marked slowing of the whole heart, and depresses auricular contractility.

FIG. 3. From the same case as Fig. 2. Compression of the left vagus does not inhibit the heart.

PLATE 2, FIG. 4. Compression of the right vagus slows the whole heart, and causes pronounced depression of auricular contractility. The inhibitory effects begin to pass off before the compression is withdrawn.

FIG. 5. Compression of the right vagus causes a moderate degree of slowing of the whole heart, and depresses auricular contractility. The retardation begins to pass off during the period of compression, but auricular contractility is not fully recovered at the close of the record. From the same case as Fig. 4.

FIG. 6. Strong inhibition by compression of the right vagus. Auricular rate and contractility are much depressed, the auricular deflexions are of abnormal form, and one ventricular systole is lengthened. The ventricular contractions following *P 4* and *P 6* are probably idio-ventricular, while the succeeding ventricular systole begins 0·31 sec. after the commencement of *P 7*. From the same case as Figs. 4 and 5.

PLATE 3, FIG. 7. Each ventricular extra-systole occurs at the same time as a physiological contraction of the auricles. The subsequent auricular contraction is premature and is represented by an inverted deflexion, *P*. Compression of the right vagus.

FIG. 8. Compression of the right vagus causes standstill of the whole heart. The first auricular deflexion after standstill for 4·44 sec. is as large as those preceding the compression.

PLATE 4, FIG. 9. Prolonged standstill of the whole heart by compression of the right vagus. After standstill for 4 sec., the auricles escape, and contract twice before the ventricles respond. The respiratory movements were recorded by means of a tambour connected with a rubber bag that was strapped to the patient's chest. The time-marker records 0·5 sec.

FIG. 10. Compression of the left vagus causes marked depression of auricular contractility, but only slight slowing of the heart.

FIG. 11. Record taken twenty minutes after 0·02 grain of atropin sulphate. The coupled rhythm still persists. The auricular rate is 97·9 per minute.

PLATE 5, FIG. 12. From the same case as Fig. 11. Record forty-eight minutes after injection of atropin. There is an occasional ventricular extra-systole. The rate of the heart is 100·8 per minute.

FIG. 13. Slow, arrhythmic oscillations. A more pronounced difference of potential ensues after compression of the right vagus. The time-marker records 0·5 sec.

FIG. 14. Slow difference of potential during and after right vagus compression. The time-marker records 0·5 sec. (p. 57).

PLATE 6, FIG. 15. Tracing from the apex-beat. Compression of the right vagus slows the whole heart and lengthens the *As–Vs* interval from 0·08 to 1·0 sec. The time record is 0·2 sec.

FIG. 16. Tracing from the brachial artery. Compression of the right vagus slows and strengthens the pulse-beats. Between five and six seconds after release of pressure there is an extra-systole, followed by a pause that is not fully compensatory. The succeeding pulse-beats show alternation. The time record is 0·2 sec.

FIG. 17. Ventricular standstill for three seconds by right vagus compression terminates with a contraction as strong as those following it.

FIG. 18. Compression of the right vagus causes pronounced inhibition. During ventricular escape there is an ascending staircase.

PLATE 7, FIG. 19. Strong inhibition of auricles and ventricles by compression of the right vagus. After standstill for 4·2 sec. the auricles escape. The second auricular beat after standstill is followed by a weak ventricular contraction, causing a small pulse-wave in the carotid artery but none in the brachial. The ventricular contractions become successively stronger, as indicated by the ascending staircase. The period during which pressure was applied is shown by the marks *. From the same case as Figs. 17, 18, and 20.

FIG. 20. From the same case as Figs. 17, 18, and 19. The inhibition by compression of the left vagus is less effective than that of the right vagus.

FIG. 21. Right vagus compression causes diminution in amplitude of the pulse without retardation (p. 64).

FIG. 22. Brachial tracing. After withdrawal of pressure from the right vagus there is an extra-systole, followed by a pause that is not fully compensatory (p. 66).

PLATE 8, FIG. 23. Diagram showing auricular acceleration after 0·02 grain of atropin sulphate. The ventricular rate is not increased. From a case of complete auriculo-ventricular dissociation.

FIG. 24. Diagram to show the rate per minute of auricles, *A*, and of ventricles, *V*, and the *a–c* interval before and after 0·03 grain of atropin sulphate in a case of digitalis heart-block. The initial effect of the atropin on the conductivity of the auriculo-ventricular bundle is shown by a lengthening of the *a–c* interval from 0·20 sec. to 0·32 sec. Seven minutes after the injection the *a–c* interval begins to lessen, until at the 16th minute it is 0·15 sec. The auricular acceleration is preceded by an initial phase of retardation which begins to pass off at the 7th minute. From the 3rd to the 7th minute there is partial heart-block.

FIG. 25. Injection of 0·025 grain of atropin sulphate. The upper curve shows the ventricular rate per minute; the lower curve indicates the number of extra-systoles per minute. There is a transient abolition of the extra-systoles after injection of atropin.

FIG. 26. Diagram of the pulse-rate per minute in a case of auricular fibrillation with a constant coupled rhythm due to strophanthus. The marks ⊙ indicate that the ventricular beats were coupled. After two injections of atropin the coupled rhythm was abolished, although the ventricular rate was not accelerated.

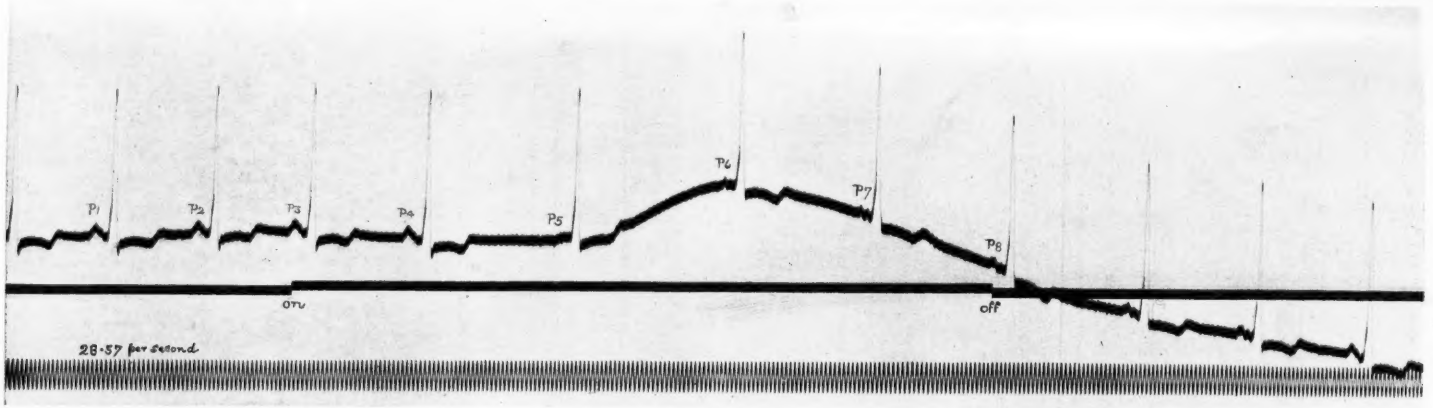


FIG. 1

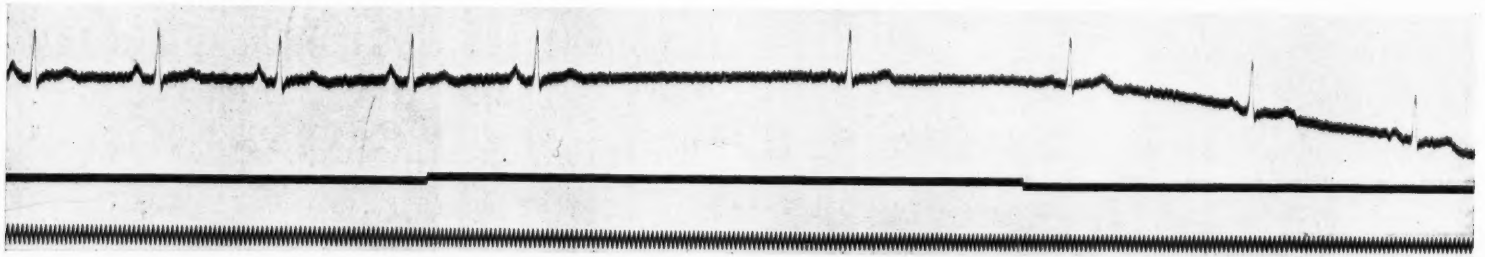


FIG. 2

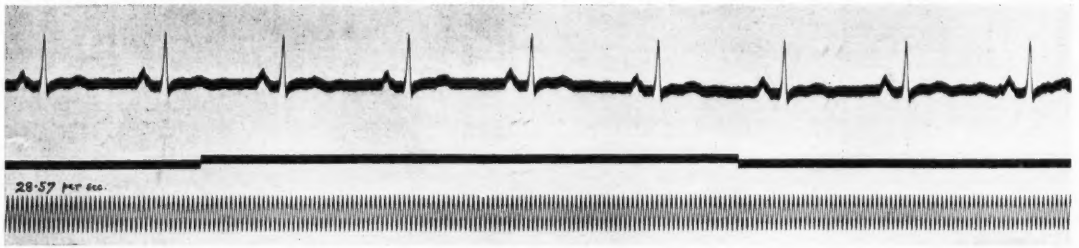


FIG. 3

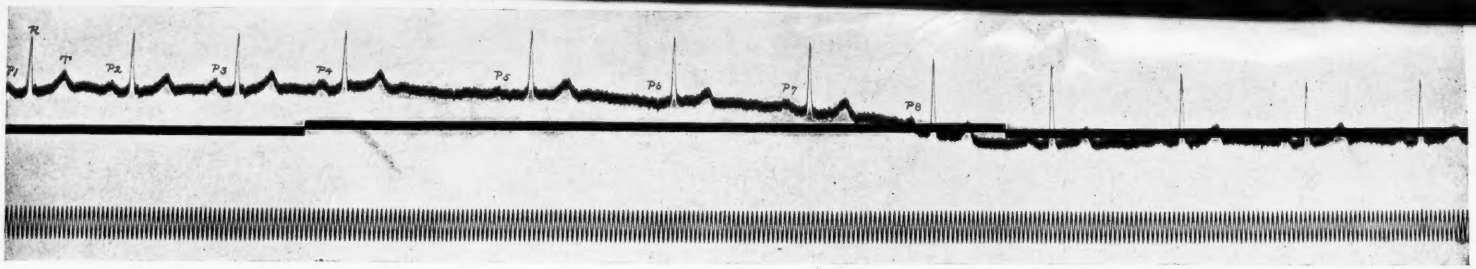


FIG. 4

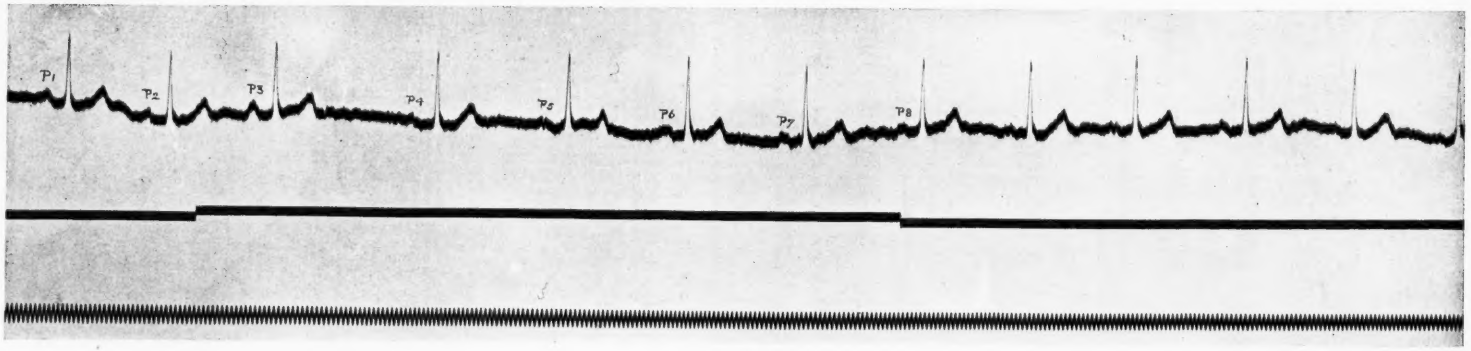


FIG. 5

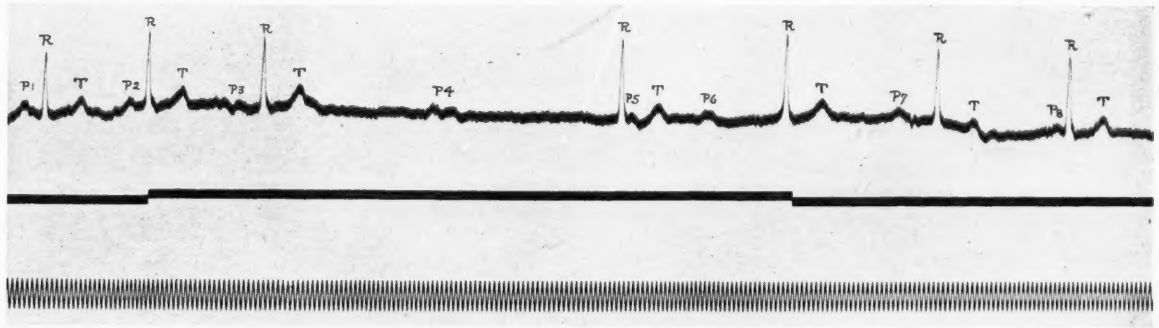


FIG. 6

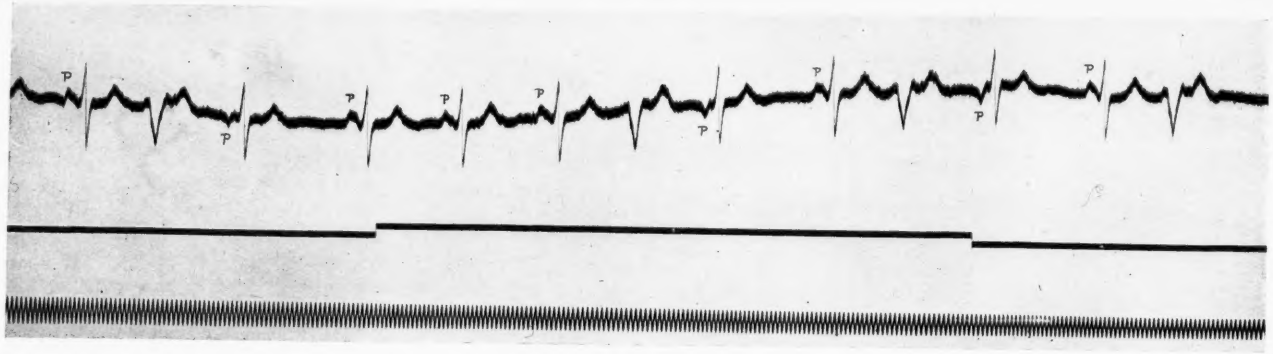


FIG. 7

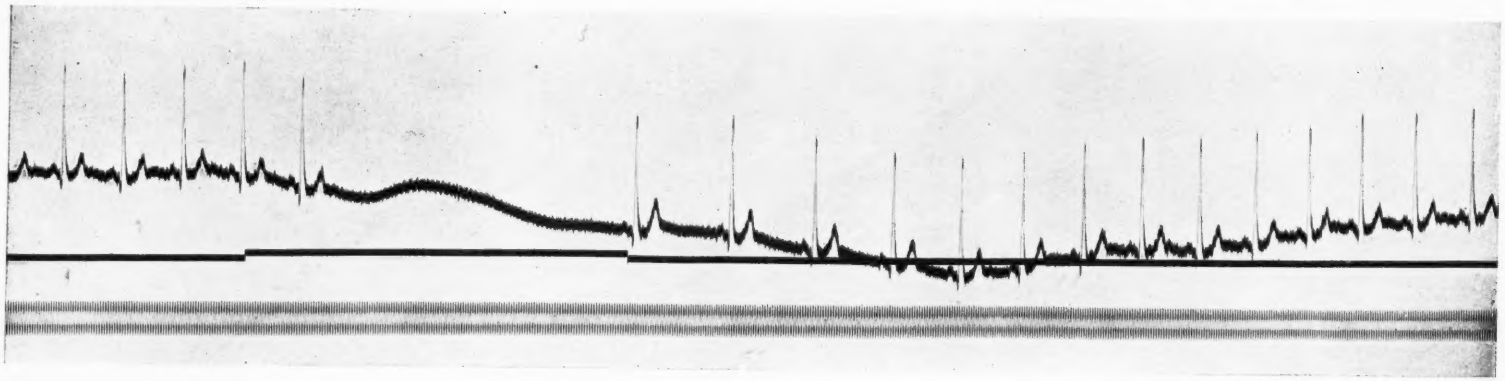


FIG. 8

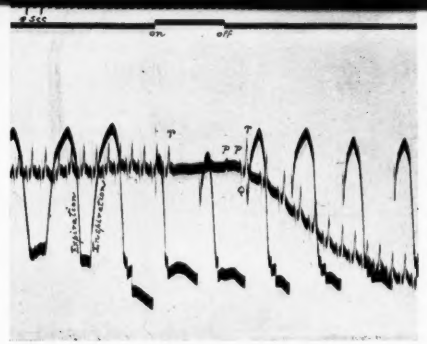


FIG. 9

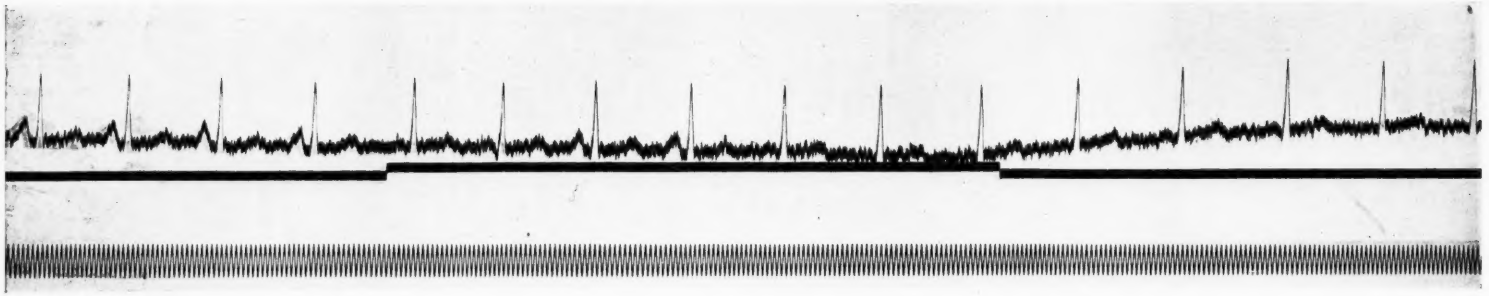


FIG. 10

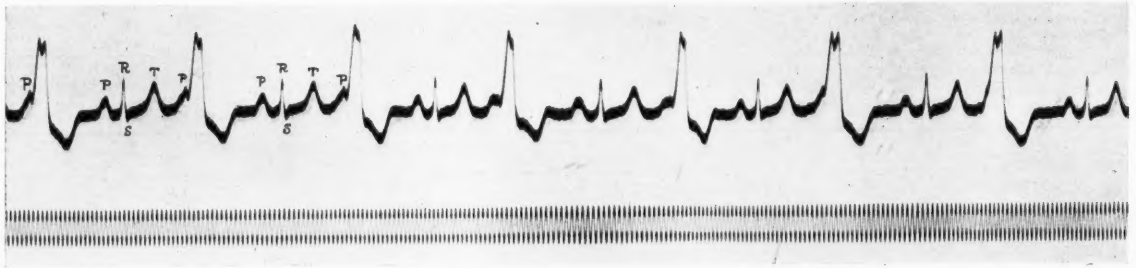


FIG. 11

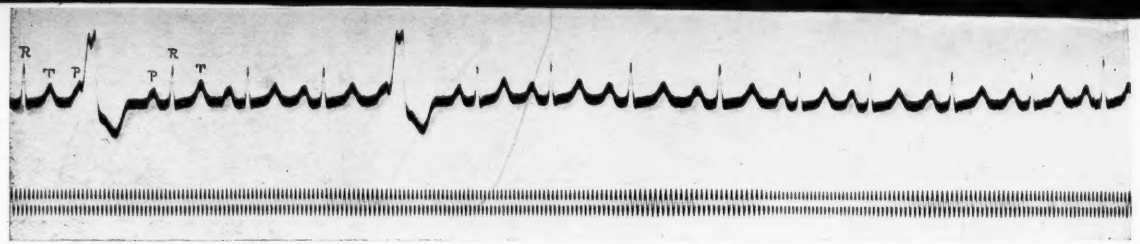


FIG. 12

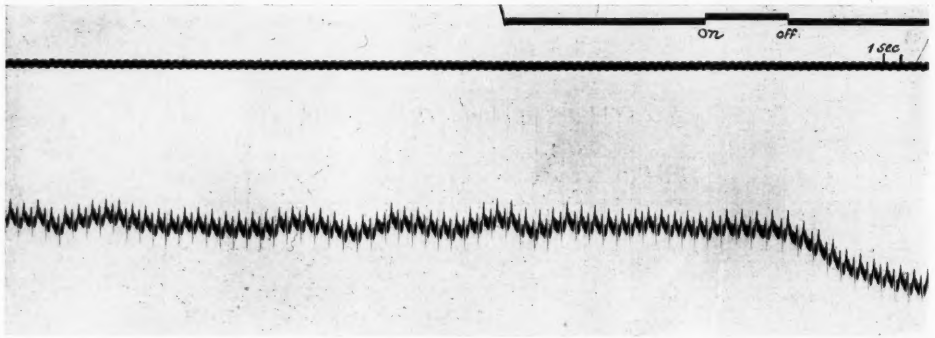


FIG. 13

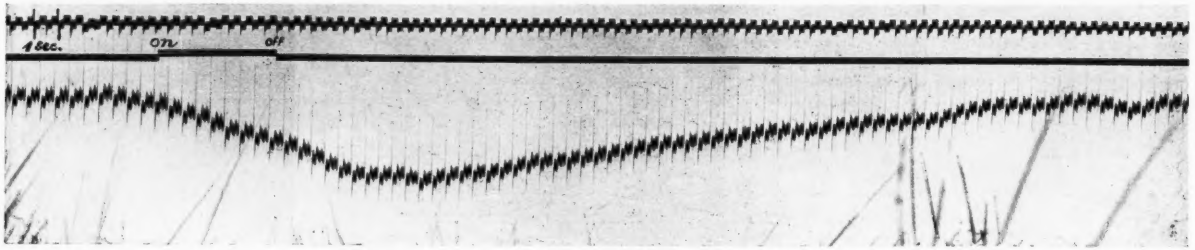


FIG. 14



FIG. 15



FIG. 16



FIG. 17



FIG. 18

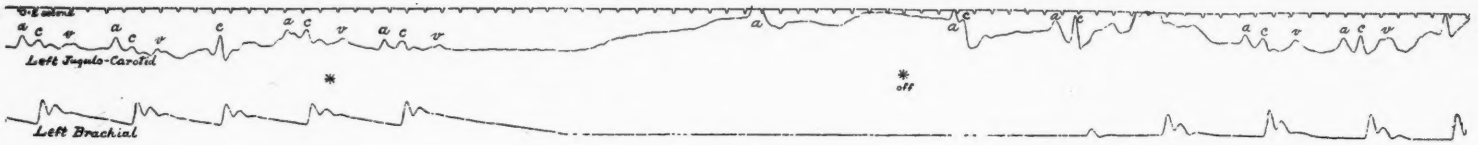


FIG. 19



FIG. 20

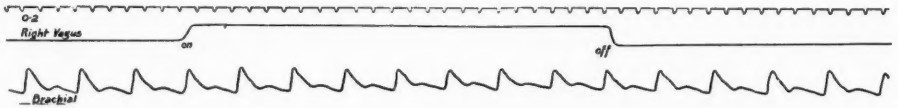


FIG. 21



FIG. 22

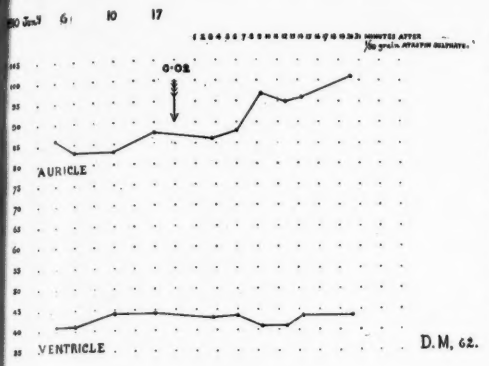


FIG. 23

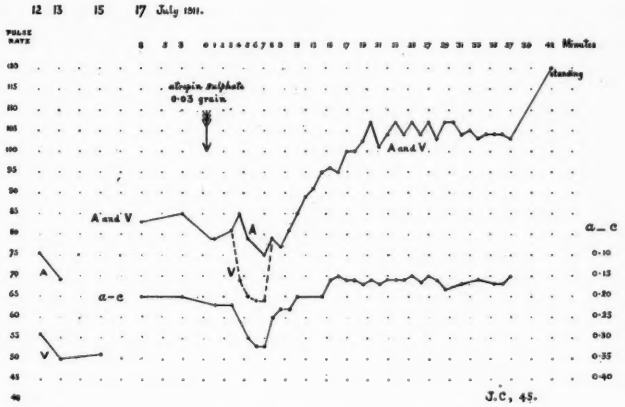


FIG. 24

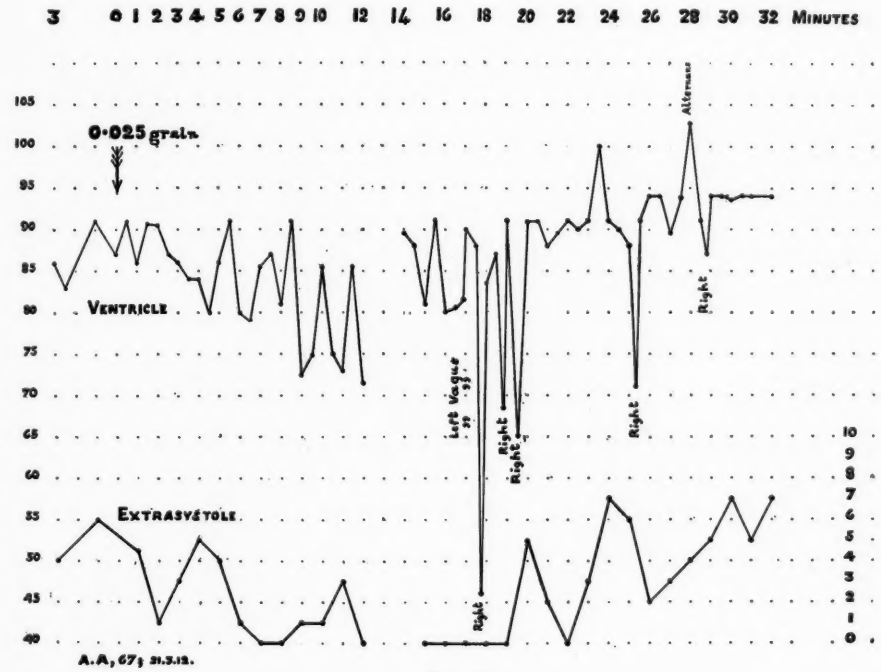


FIG. 25

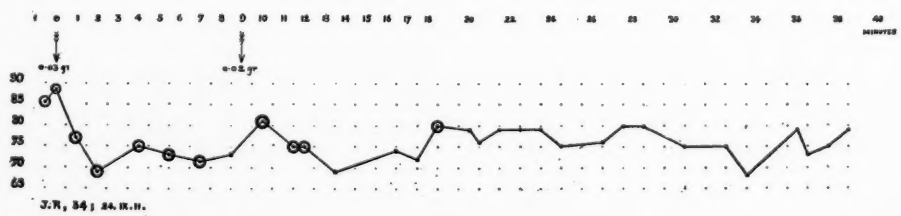


FIG. 26

INVESTIGATIONS ON THE GASTRIC JUICE IN MALIGNANT AND NON-MALIGNANT DISEASES OF THE STOMACH AND DUODENUM

PART I. ON A PEPTOLYTIC ENZYME OF GASTRIC JUICE[1]

By S. B. SCHRYVER AND CHARLES SINGER
(From the Research Institute of the Cancer Hospital)

Some three years ago Otto Neubauer and Hans Fischer (1) showed that the gastric juice in many cases of carcinoma of the stomach contained an enzyme capable of hydrolysing glycyltryptophan, and they suggested a simple method of detecting the ferment for diagnostic purposes. Since then several papers dealing with the subject have appeared, the most noteworthy being those of Lyle and Kober (2) and Walker Hall and Williamson (3).

Recently Koelker (4) and Warfield (5) have independently put forward the suggestion that this ferment reaches the stomach from the *saliva*. According to their view the ferment remains stable in the weakly acid contents of certain pathological cases, but is destroyed by higher degrees of acidity. Neubauer and Fischer (1), however, had already pointed out that as much as 0·36 per cent. of hydrochloric acid was necessary to render their test negative, a percentage only encountered in highly acid gastric juices.

On the other hand, it is probable that the ferment is not of *duodenal* origin, for Abderhalden and Medigreaceanu (6) have demonstrated that the true tryptic ferment of the duodenum is quickly killed by the normal gastric acidity. Finally, Weinstein (7), dissatisfied with the uncertainty of the glycyltryptophan test, has introduced another and simpler method of utilizing the 'tryptophan reaction.' He claims that if gastric juice from a case of carcinoma of the stomach be merely incubated, tryptophan will be set free and will show its typical reaction. This he attributes to the action of the ferment on certain substances naturally present and allied in structure to the glycyl compound. He admits that the reaction does not occur in every case, but claims that, in a series of some extent, positive results were obtained only in cancerous cases.

The present communication deals with the existence in certain gastric

[1] We have to thank Dr. P. N. Panton, Clinical Pathologist to the London Hospital, who with great courtesy and generosity has provided us with a series of samples of gastric juice. We have also to thank members of the staffs of the London, Dreadnought, and Cancer Hospitals, whose material has been utilized by us in the course of this research.

contents of a ferment of more general character than that discussed by these writers, a ferment capable of further digesting proteins previously degraded as far as possible by means of pepsin. It will be seen that a ferment of this peptone-splitting character is not necessarily identical with the enzyme which hydrolyses a *specific* peptide (as is suggested with regard to the ferments of human pancreatic juice by Wohlgemuth's (8) recent investigations).

For the purpose of our experiments ordinary Witte's peptone was used. It was hoped that with this cheap and accessible laboratory substance a test might be evolved of more general utility than one demanding a material so rare and difficult to prepare as glycyltryptophan. Peptone incubated with pepsin or normal gastric juice undergoes no further degradation and is unchanged, except for the very slight extent to which it is acted upon by the medium in which it is dissolved. There are, however, certain *pathological* cases in which, as will be seen in the sequel, the gastric juice may contain a ferment capable of hydrolysing and thus further degrading peptone, provided the medium be not too strongly acid.

For the purpose of investigating this change, the Sörensen-Schiff formaldehyde titration method was employed. This method depends on the power of an aldehyde to alter the reaction of a neutral or amphoteric substance containing both an amino (NH_2) and a carboxyl (COOH) group. When such a substance is titrated with an alkali, its reaction is found to be neutral or very faintly acid. On adding formaldehyde, however, the aldehyde enters into reaction with the amino group, giving rise to methyleneimino acid, in which the basic character of the amino group is no longer in evidence. Such a substance has a decided *acid* reaction and its acidity can be estimated by titration with an alkali.

In the case of the simplest amino acid, glycocol (glycine), this reaction can be represented as follows:

$$CH_2(NH_2)\cdot COOH + HCHO = H_2O + CH_2(N:CH)\cdot COOH \qquad (A)$$

Now a peptone consists of a mixture of amino acids and a number of more or less complicated substances with the essential character of polypeptides. These latter are formed by the congregation together of two or more amino acids. Thus two molecules of glycine can be coupled together to form glycylglycine, which is the simplest example of a polypeptide:

$$CH_2(NH_2)\cdot COOH + CH_2(NH_2)\cdot COOH = H_2O + CH_2(NH_2)\cdot CO\cdot NH\cdot CH_2\cdot COOH \qquad (B)$$

Conversely, on hydrolysis, glycylglycine will undergo scission into two molecules of glycine:

$$CH_2(NH_2)\cdot CO\cdot NH\cdot CH_2\cdot COOH + H_2O = 2\ CH_2(NH_2)\,COOH \qquad (C)$$

Further, glycylglycine, on treatment with formaldehyde, will give a methyleneimino derivative, according to the following equation:

$$CH_2(NH_2)\cdot CO\cdot NH\cdot CH_2\cdot COOH + HCHO = CH_2(N:CH)\cdot CO\cdot NH\cdot CH\cdot COOH + H_2O \qquad (D)$$

in which the amino group (NH_2) is replaced by a methyleneimino (N:CH) grouping. Every molecule of such a substance will require one molecular equivalent of sodium hydroxide to neutralize it to phenolphthalein.

Now suppose glycylglycine to undergo hydrolysis according to equation (C). It will then give rise to *two* molecules of glycine. These will react with formaldehyde to give rise to *two* molecules of methyleneimino acid. The two molecules will require just twice as much sodium hydroxide to neutralize them as the methyleneimino derivative of glycylglycine from which they have been derived by hydrolysis, for the derivative contains twice as much of the actively acid carboxyl group (COOH) as the substance that formed its source. This becomes evident from the two following equations:

$$CH_2(N:CH)\cdot CO\cdot NH\cdot CH_2\cdot COOH + 1\,NaOH = CH_2(N:CH)\cdot CO\cdot NH\cdot CH_2\cdot COONa + H_2O \qquad (E)$$

$$\begin{array}{l} \quad\quad\quad\quad + H_2O \\ \quad\quad\quad\quad\quad\downarrow \\ 2\,CH_2(N:CH)\cdot COOH + 2\,NaOH = 2\,CH_2(N:CH)\cdot COONa + 2\,H_2O \end{array} \qquad (F)$$

If now the solution of a digestion product containing polypeptides of the type of glycylglycine (though in the majority of cases in any such product the substances of this type will be far more complex) together with amino acids be treated with formaldehyde, a certain amount of sodium hydroxide will be required to neutralize it. But if such a solution be previously hydrolysed (as by a ferment) and the product be then treated with formaldehyde, a larger amount of alkali will be required for neutralization than before digestion. This is due to the scission of the peptide linkings, and the setting free of amino and carboxyl groups as acid reacting substances. The simplest example of such a change is illustrated by equation (C).

If therefore a given peptone be digested with a substance suspected to contain a peptolytic ferment, and the acidity subsequent to the addition of formaldehyde be estimated, an increase of acidity may serve to betray the presence of such an enzyme. We have investigated a large number of gastric juices for a ferment of this nature, and have succeeded in detecting it in a small percentage ($6\frac{1}{2}$ per cent.) of pathological cases, all of which were suspected on clinical grounds of abnormal gastric conditions. The ferment was found to react in alkaline or faintly acid media. Stronger acids (e.g. 10 c.c. N/10 HCl added to 20 c.c. 5 per cent. peptone solution) render it less active.

The actual method of experiment was as follows: 20 c.c. of a filtered 5 per cent. solution of Witte's peptone were mixed with 1 c.c. of the filtered juice under examination. Another sample of a similar solution was mixed with 10 c.c. N/10 sodium hydroxide solution, to which was also added 1 c.c. of the gastric juice. Similar mixtures without addition of juice were kept as controls, and all the four samples were incubated for 20 to 24 hours at 37°, with the addition of 1–2 c.c. of toluene to prevent putrefaction. After removal from the incubator, each sample was treated with 10 c.c. of 40 per cent. formaldehyde solution (commercial formalin), previously neutralized to phenolphthalein by sodium hydroxide, and containing therefore some of the indicator (about $\frac{1}{2}$ c.c. of 0·5 per cent. solution of phenolphthalein in 50 per cent. alcohol to each 10 c.c. of formalin). The formaldehyde-peptone mixture was then immediately titrated.

If the juice contained a peptolytic ferment there was a difference of 2·5 to 4 c.c. in the amount of alkali required for neutralization, between the sample containing the juice and the control. Both in the cases in which the juice contained no peptolytic ferment and in the controls, there has usually been a slight rise in acidity during incubation. This rise may be attributed to two factors. In the first instance it is in some part due to the natural acidity of the added juice, but in all cases there is also, independently of the presence of a ferment, a certain slight degree of hydrolysis on exposing a solution of peptone to 37° for a long period. On this account the use of a separate set of controls is essential for each experiment.

Samples of gastric juice from 200 cases of grave disorders of the stomach and duodenum have been investigated in the course of the work. In most cases we have relied on others for the actual removal of the gastric juice from the stomach. This operation has been performed one hour after a test meal consisting of two rounds of buttered toast and a pint of weak tea with milk and sugar added.

In each gastric juice we have investigated a number of other points besides the presence or absence of a peptolytic ferment. Among these have been :—

1. The total acidity as represented by the titration value to $\frac{N}{10}$ sodium hydroxide with phenolphthalein as an indicator.

2. The *free* HCl as represented by the titration value to $\frac{N}{10}$ sodium hydroxide with orange G (dimethylamido-azobenzene) as an indicator. [For the value of this method we refer the reader to the work of Drs. Panton and Tidy in vol. iv of this Journal (9).]

Gunzberg's test with freshly prepared reagents has also been applied in every case.

3. The total chloride and 'active chloride' estimated according to Dr. Wilcox's (10) modification of the Volhard-Luttke method.

4. The amount of nitrogen present.

5. The peptic power as estimated by Fuld and Levison's (11) method.

This last method may be unfamiliar to our readers, and as we have drawn conclusions from the results of its application, we give here a short description of the modified technique that we have adopted.

A pure preparation of edestin was obtained in the laboratory by recrystallization from warm salt solution. From this was made a solution of 0·1 per cent. of edestin in 0·12 per cent. hydrochloric acid (i.e. 30 c.c. normal HCl in 1 litre distilled water. We found that such a solution of edestin need not be made freshly for each observation, but that if used as stock it must be stored at zero temperature). Into each of 10 small test-tubes 2·5 c.c. of this solution is pipetted and left to take the temperature of the room (10°–20° C.). Into each test-tube is now dropped 0·1, 0·2, 0·3, 0·4... to 1·0 c.c. (in ascending series) of the gastric juice under investigation, previously diluted

to one-tenth of its natural strength. Each test-tube is shaken and left to stand. After thirty minutes have elapsed 0·3 c.c. of a saturated solution of sodium chloride is added to each tube. If digestion has proceeded to a certain point the solution remains clear, while with lower degrees of digestion a white cloudiness immediately develops.

We designate as the *Peptic Index* in any case the number of tenths of a c.c. of a diluted juice added to the first clear test-tube and divided into 100. This gives as a range of possible readings the ten numbers 100 (i. e. $\frac{100}{1}$), 50 (i. e. $\frac{100}{2}$), 33 (i. e. $\frac{100}{3}$), 25, 20, 17, 14, 12, 11, and 10. For greater accuracy intermediate amounts of diluted gastric juice may be added, as 0·125, 0·150, 0·175 (between 0·1 and 0·2), &c., but with practice it becomes possible to read such intermediate numbers without recourse to actual experiment. Cases do occasionally present themselves with an index above 100 (i. e. in which even the test-tube containing only 0·1 c.c. of diluted juice remains clear on the addition of the salt solution). In such instances recourse must be had to the use of more diluted juice. At the other extreme, however, it is seldom necessary to take readings below an index of 10 (i. e. in which even the test-tube containing 1·0 c.c. of diluted gastric juice develops cloudiness on the addition of salt solution), for in such cases our experience seems to show that digestive power is probably almost absent.

In the 200 cases investigated we have found a peptolytic ferment in seventeen. Of these, however, four were patients in whom the operation of gastroenterostomy had been performed and the ferment was therefore regarded as of duodenal origin. The remaining thirteen cases, forming $6\frac{1}{2}$ per cent., are a homogeneous group with the following well-marked characteristics, which cannot be explained as a result of duodenal regurgitation:

1. The total acidity is low in all, and very low in all except IX and XII. (In Case XII, the acidity of which was the highest of our series, there was evidence that much of the acidity was due to lactic and butyric acids.)

2. In every case except X the Gunzberg test for free HCl was negative. In Case X itself the reaction was exceedingly faint and only doubtfully positive. The dimethyl test for free hydrochloric acid (which, for reasons discussed in another communication, we regard as rather more delicate than Gunzberg's) showed a measurable quantity of HCl in only two cases, Nos. X and XI.

3. The amount both of total and active chloride was below normal in every case except one (No. IX), and in several instances was so low as to suggest the complete absence of all active secretion and a condition of achylia. The exceptional case, IX, obtained from a patient with mucous colitis, showed several other anomalous features.

4. The peptic index was very low in all. In seven cases it was certainly less than 10 and probably very near zero. In only one of the remaining cases did the index rise even to 25. (The average of healthy cases we estimate to be about 50.)

These observations are set forth in the accompanying Table A. The last two columns indicate the increase of acidity in an incubated specimen of peptone,

TABLE A

Analytical results obtained from 13 cases in which a peptolytic ferment was present in the gastric juice. All numbers except the nitrogen content and peptic index are expressed in their equivalent of decinormal sodium hydroxide in 10 c.c. of the juice. The numbers in the nitrogen column represent the number of c.c. of decinormal sulphuric acid necessary to neutralize the ammonia obtained by Kjeldahlizing 10 c.c. of gastric juice.

Case No.	Sex.	Symptomatic Diagnosis.	Pathological Diagnosis.	Phenol Acidity.	Dimethyl Acidity.	Gunzberg.	Peptic Index.	Total Chloride.	Active Chloride.	Nitrogen.	Difference A (with 10 c.c. N/10 NaOH added).	Difference B.
I.	M.	Achylia	—	1·4	0·0	–	<10	Neg.	Neg.	Neg.	3·3	4·5
II.	F.	Achylia	Dilated stomach. Benign stricture of pylorus	0·9	0·0	–	<10	Neg.	Neg.	Neg.	3·1	3·0
III.	M.	Achylia	—	1·1	0·0	–	<10	Neg.	Neg.	Neg.	3·1	3·0
IV.	M.	Dyspepsia	—	1·6	0·0	–	15	Neg.	Neg.	Neg.	5·0	4·2
V.	M.	Achylia	Carcinoma of cardiac end of stomach	2·1	0·0	–	<10	1·9	0·4	Neg.	3·9	3·9
VI.	M.	Apepsia	Dilated stomach	2·7	0·0	–	<10	5·6	2·7	7·1	2·4	3·7
VII.	M.	Achylia	Dilated stomach. Carcinoma of stomach.	1·6	0·0	–	<10	4·6	1·7	Neg.	2·9	3·0
VIII.	M.	Achylia	—	0·5	0·0	–	<10	2·2	1·2	Neg.	2·1	3·0
IX.	M.	Dyspepsia	Mucous colitis	3·7	0·0	–	20	7·1	5·4	11·7	2·1	3·0
X.	F.	Dyspepsia	Dilated stomach	2·2	1·1	+?	12	3·5	2·6	4·5	2·3	3·7
XI.	F.	Dyspepsia	Dilated stomach. Carcinoma of pylorus	2·6	0·6	–	25	5·6	1·4	6·7	2·4	4·8
XII.	M.	Dyspepsia	Dilated stomach	4·4	0·0	–	16	5·3	3·3	12·8	2·7	3·9
XIII.	F.	Dyspepsia	Dilated stomach. Carcinoma of Duodenum	2·6	0·0	–	12	5·8	2·2	6·9	3·0	3·4
Average				2·1	0·1	–	7 to 13	4·6	2·3	8·3	3·0	3·4
Healthy case				5·0	3·0	+	40 to 60	8·0	5·0	8·0	0·5	0·5

to which gastric juice has been added and the mixture subsequently treated with formalin. The technique of the process has already been described on pages 73 and 74. In each case two observations were made, one with the previous addition of 10 c.c. of decinormal sodium hydroxide and the other without that addition. For convenience and comparison we have added the readings of a normal healthy case and appended in Table B readings taken from four cases in which the operation of gastroenterostomy had been performed some time previously.

TABLE B.

Analytical results obtained from four cases on which the operation of gastroenterostomy had been performed.

Case No.	Phenol Acidity.	Dimethyl Acidity.	Gunzberg.	Peptic Index.	Total Chloride.	Active Chloride.	Nitrogen.	Difference A (with 10 c.c. N/10 NaOH added).	Difference B.
XIV.	5·6		–	Neg.	Neg.	Neg.	Neg.	5·1	4·4
XV.	0·0	0·0	–	<10	Neg.	Neg.	Neg.	14·8	11·5
XVI.	1·1	0·0	–	<10	Neg.	Neg.	Neg.	2·0	1·3
XVII.	1·9	0·3	–	16	8·0	1·5	6·0	2·1	3·1

It will be seen from Table A that whereas there was considerable similarity in the actual composition of the gastric juice of the thirteen cases, there was great diversity in the disease from which the patients were suffering. The actual results of gastric analysis would, we think, in every case be usually regarded as suggestive of or at least consistent with the diagnosis of carcinoma ventriculi, and that was the provisional judgement given in most instances. Nevertheless, in only four of the thirteen cases was a malignant growth present, and in one of these the growth was situated not in the stomach but in the duodenum, taking its origin at the ampulla of Vater. In one case, exceptional also in other respects, the patient was a sufferer from mucous colitis. In three others the stomach was markedly dilated, without assignable cause, and in one there was a benign stricture of the pylorus. In the remaining four cases, however, the only diagnosis possible, even after operation and examination of the gastric juice, was a symptomatic condition for which no underlying pathological cause could be detected.

The presence of the peptolytic ferment is certainly not characteristic of carcinoma of the stomach, for in twenty-five unequivocal cases of that disease to which we have applied the test we have obtained a positive result in only the three quoted. Coarse ulceration of a non-malignant character was not found associated with this ferment among our cases.

The commonest feature of the group was a dilated condition of the stomach, which was certainly present in seven of the thirteen cases and may have been a factor in others. In several, however, this feature seemed to be absent. In both the cases which came to post-mortem (Nos. II and XIII) gastric dilatation was a marked feature and the mucous membrane of the stomach was smooth and

pigmented. We have been unable to gain evidence of the presence of the ferment in the saliva, and have only negative results to report for a number of cases tested. In this respect our results are in accord with those of Weinstein (7), who also failed to obtain his tryptophan test with saliva.

Lastly, we may add that in two cases, Nos. XII and XVII (the latter a case of gastroenterostomy suffering from stenosis of the artificial opening into the intestine), we have applied the glycyltryptophan test with negative results.

Provisionally, therefore, we regard this peptolytic ferment as of local origin, associated with well-marked symptoms and with changes in the gastric juice caused by some hitherto undetected alteration in the secretory mechanism of the stomach wall, and probably related to the process of gastric dilatation.

Conclusions.

1. In about $6\frac{1}{2}$ per cent. of cases of grave gastric disorder a ferment is present in the gastric juice capable of hydrolysing Witte's peptone.

2. This abnormal ferment is of unknown origin. Apparently, however, it is derived neither from the duodenal secretion nor from the saliva, but from the stomach itself. It has been detected only in cases with severe dyspeptic symptoms.

3. The gastric juices in which the ferment has been detected have been uniformly characterized by their poor hydrochloric acid content and low or absent peptic power. In most of the cases, moreover, an extremely low gastric secretory power has been suggested by the small amount of chlorides present.

4. The abnormal ferment is neither peculiar to nor characteristic of gastric carcinoma. In the majority of cases in which carcinoma was undoubtedly present the peptolytic ferment was absent.

5. The commonest condition associated with the ferment appears to be gastric dilatation with atrophy of the walls of the stomach and thinning of the mucous membrane. This condition was present in at least seven of thirteen cases and in two that came to post-mortem.

We have examined the diagnostic value of various other factors in the composition of gastric juice. These we propose to discuss in a subsequent communication.

Appendix.

Clinical notes on thirteen cases in which a peptolytic ferment was detected in the gastric juice. The analytical results of the examination of the gastric juices will be found in Table A on page 76.

I. Male, aged 59. Lighterman. *Symptoms.* Epigastric pain for four months following a blow. The pain came on immediately after food and was not relieved by alkalis. Patient was a pinched-looking subject with defective circulation. Shortly after admission to hospital he exhibited a transient glycosuria. Marked loss of weight during previous few months with occasional vomiting not definitely related to food. *Operation.* Laparotomy. Stomach normal. No abdominal disease detected. *Diagnosis.* Achylia.

II. Female, single, aged 42. Dressmaker. *Symptoms* had been present for two years. The patient during this time had had attacks of pain and vomiting every three or four weeks. The pain was at first epigastric, but gradually settled lower in the abdomen. Constipation had been a troublesome feature throughout, becoming progressively more severe. Vomiting had been frequent and had usually taken place immediately after food. The pain, however, had had only an indefinite relationship to meals. *Operation.* Laparotomy. Multiple adhesions were present and were especially marked in the pelvic region. The patient died of shock very shortly after operation. *Post-mortem.* An extensive chronic peritonitis. There were multiple frail adhesions between the omentum and the anterior parietal peritoneum. There were also adhesions between the coils of gut, especially in the pelvis and in the region of Douglas's pouch. At the bottom of the pelvis there was a mass of intestines densely adherent to the rectum, and here a natural fistula had formed between the small intestine and the sigmoid flexure. The *stomach* was much dilated and its walls very thin. The mucous membrane of the stomach was smooth and showed numerous areas of pigmentation. *Diagnosis.* Chronic general peritonitis. Benign stricture of pylorus and extreme gastric dilatation.

III. Male, aged 50. Boiler-maker. *Symptoms.* History of about four years' duration, during which he had been getting progressively worse. Epigastric pain immediately below xiphisternum came on immediately after food and lasted 2 to 2½ hours, but disappeared when stomach was empty. Worse after solids than after liquids. Pain relieved by pressure, but not by food or alkalis. Latterly, pain had been practically invariable after all food. Loss of weight amounting to 3½ stone in a year. Tabes dorsalis excluded. No vomiting. Patient responded to treatment and went out free from symptoms. *Operation.* Laparotomy. No growth or ulcer present. Nothing abnormal observed. *Diagnosis.* Achylia.

IV. Male, aged 27. Packing-case maker. *Symptoms* commenced eighteen months before admission and followed a febrile attack. The first symptoms were flatulent distension and epigastric pain passing into right shoulder. On admission the right rectus abdominis was held rigid and abdominal palpation was difficult. The patient had been suffering from severe griping abdominal and epigastric pain for fourteen days previously. This was a typical attack, and he had had many such. It gradually cleared up with rest in bed and simple purgative treatment. There was nothing in his manner of life or diet to explain the onset of his symptoms. No operation was performed. *Diagnosis.* Dyspepsia.

V. Male, aged 43. Stevedore. *Symptoms* of eight months' duration. Pain chiefly referred to shoulder region and later to epigastrium. Pain gnawing in character and not related to food nor relieved by it. Coffee-ground vomit on several occasions. Much wasting. Loss of 4 lb. weight in one week. *Radiograph* with bismuth meal. The lower border of the stomach was seen two inches above umbilicus. There were good contractions and no irregularity of gastric outline. Bismuth was seen passing through pylorus. *Operation.* Laparotomy. An extensive growth was present involving the cardiac region of the stomach, and with infiltration of glands of lesser curvature. Enlarged glands along pancreas and growth extending right up to oesophagus. Inoperable. *Diagnosis.* Achylia. Carcinoma cardiac end of stomach.

VI. Male, aged 69. Labourer. *Symptoms* had been present for twelve months. At first there was a slight epigastric burning sensation not very definitely related to food. After a time this developed into great discomfort, which was occasionally relieved by vomiting. When he presented himself at hospital the vomiting was frequent and copious, and often consisted of a meal

that had been taken some time before. Thus, for instance, a currant was vomited five to six hours after ingestion. Rapid loss of weight. The stomach was prominent and dilated as regards its percussion area. The patient distinctly improved with dieting, rest, and hospital treatment, and went out free from symptoms. *Diagnosis.* Apepsia. Dilated stomach.

VII. Male, aged 60. *Symptoms.* Had all his life suffered with dyspepsia. For nine months previous to admission had much pain at a variable time after food. The pain was eased by vomiting or by taking chlorodyne. Patient had often deliberately made himself sick. Vomit very copious. On admission the patient had numerous small hard glands on the left side of the neck and in the left axilla. There was a large irregular tumour to be felt in the region of the epigastric and right hypochondriac region. The tumour moved during respiration. Much wasting. The signs and symptoms left no doubt that the patient was suffering from carcinoma of the stomach with metastasis formation. Operation was not considered justifiable. *Diagnosis.* Achylia. Dilated stomach. Carcinoma of stomach.

VIII. Male, aged 59. Stone-mason. *Symptoms.* Long but indefinite history of 'indigestion', which had become worse during the last ten months. He had an epigastric dragging pain only relieved by rest. The discomfort had very little relation to food. *Operation.* Laparotomy. The stomach presented a healthy appearance. No disease found except long appendix full of faecal matter with some adhesions. *Diagnosis.* Achylia.

IX. Male, aged 34. Clerk. *Symptoms* for two years. The trouble commenced with pain during the taking of food, and after food with flatulence and constipation. Repeated attacks of this sort lasting about a week or ten days, and these attacks had been getting more frequent and the constipation more obstinate. The stools contained considerable quantities of mucus. The sigmoidoscopic examination was negative. There was a constant tender area in the left iliac fossa. Responded well to treatment. *Diagnosis.* Dyspepsia. Mucous colitis.

X. Female, single, aged 22. Office cleaner. *Symptoms.* For eight months had been subject to pain after food varying in time from immediately subsequent to half an hour after. Pain lasted about an hour and often terminated in vomiting. There was bulging in the epigastric region and splashing sounds. The stomach was dilated as judged by percussion and auscultation. The patient's condition greatly improved with alkalis and regular purging. *Diagnosis.* Dyspepsia. Dilated stomach.

XI. Female, married, aged 53. Housework. *Symptoms.* For the last few months had been vomiting occasionally. Of late the vomiting had become much more frequent and usually took place about half an hour after food. Much burning epigastric discomfort and pain in the throat, usually relieved by vomiting. A hard, irregular, movable lump could be felt in right hypochondriac region about the size of an orange. *Operation.* Laparotomy. Extensive carcinoma of stomach. Metastases in liver; hopelessly inoperable. Stomach large. *Diagnosis.* Dilated stomach. Carcinoma of pylorus.

XII. Male, aged 32. Labourer. *Symptoms.* For two years, greatly accentuated for last three months. There had been loss of appetite and marked wasting with attacks of epigastric pain, occasionally becoming very severe and exhausting. Vomiting occasional. About three months ago had a severe haematemesis during which he brought up two pints of blood and was in hospital for some weeks. Pain half-hour after food and lasting an hour. Pain also about 2 a.m. A few weeks ago he had another attack of vomiting. On this occasion he brought up much coffee-ground material and had definite melaena. *Operation.*

Laparotomy. Stomach dilated. Nothing else found. *Diagnosis.* Dyspepsia. Dilated stomach.

XIII. Female, aged 58. Married. *Symptoms.* For two years before admission to hospital, patient had attacks of abdominal pain from time to time. These attacks had been more frequent and more severe for the last eight months. About six weeks before patient was seen, vomiting about half an hour after food commenced, and she became very constipated. There was never any haematemesis, the tongue remained clean throughout, and the pain was only indefinitely related to food. It was thought that a hard fixed mass could be felt descending from the subcostal margin. The stomach was dilated and visible gastric peristalsis was present. No jaundice. *Operation.* Laparotomy. The stomach appeared only slightly fallen and not greatly dilated. The greater curvature appeared to have descended only about $1\frac{1}{2}$ inches below the umbilicus. The abdomen was carefully searched, but no growth or ulcer was found, though what appeared to be a mass of glands was felt in the mesentery. After the operation the patient passed into a comatose state and died in a few days. *Post-mortem.* A malignant ulcer with raised and everted margin was found in the region of the papilla of Vater in the second part of the duodenum. The base of the ulcer was adherent to the pancreas. The ampulla of Vater and the duct of Vieussens opened outside the margin of the ulcer. The bile duct was patent. The stomach was dilated. *Diagnosis.* Dyspepsia. Dilated stomach. Primary carcinoma of duodenum.

BIBLIOGRAPHY.

1. Neubauer, O., und Fischer, H., *Deutsch. Archiv f. klin. Med.*, 1909, xcvii. 499.
2. Lyle, W. G., and Kober, P. A., *New York Med. Journ.*, 1910, xci. 1151.
3. Hall, I. W., and Williamson, G. S., *Lancet*, Lond., 1911, i. 731.
4. Koelker, A. H., *Zeitsch. f. physiol. Chemie*, Strassburg, 1911, lxxvi.
5. Warfield, *Bull. Johns Hopkins Hosp.*, Baltimore, 1911, xxii. 150.
6. Abderhalden, E., und Medigreaceanu, F., *Zeitsch. f. physiol. Chemie*, Strassburg, 1908, lvii. 317.
7. Weinstein, J. W., *Journ. of the Amer. Med. Assoc.*, 1910, lv. 1085, and 1911, lvii. 1420.
8. Wohlgemuth, J., *Biochem. Zeitsch.*, Berlin, 1912, xxxix. 302.
9. Panton, P. N., and Tidy, H. L., *Quart. Journ. Med.*, Oxford, 1910–11, iv. 449.
10. Willcox, W. H., *Lancet*, Lond., 1905, i. 1566.
11. Fuld und Levison, *Biochem. Zeitsch*w., Braunschw., 1906, 473.

THE INFLUENCE OF HIGH TEMPERATURE ON PROTEIN METABOLISM WITH REFERENCE TO FEVER

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Historical.

The increase of protein destruction in fever has long been established, and has been ascribed to such causes as toxic action, inanition and the deleterious action of the high temperature itself.

The toxic destruction of proteins in fever has been advocated among others by Friedrich Müller (29) and Krehl (16). These authors have thought that the agent causing the fever actually destroys the cell proteins in various parts of the body.

Richard May (24) has shown that, in fever, the carbohydrate metabolism is greatly increased. A deficiency of glycogen rapidly occurs, and the body proteins are then called upon to take a large share in providing fuel for the increased energy production. That this state of febrile inanition plays a great part in the increased protein destruction has been shown by Schaffer and Coleman (34), who succeeded in maintaining typhoid patients in nitrogen equilibrium by feeding them with a large excess of carbohydrates together with an adequate supply of protein. Grafe (9) has recently suggested that the high protein metabolism in fever is not due to toxic action, and may be entirely accounted for by the deficiency in carbohydrate metabolism.

The influence of high temperature on the protein metabolism in healthy men and in animals has been frequently investigated, but with conflicting results. An account of the earlier work is given by Simanowsky (36). Kaupp, and later Koch, found that there was no increase in the protein metabolism, as a result of an artificially produced high temperature. However, Bartels, Naunyn, Schleich, Frey and Heiligenthal found that an increase occurred. These results are not very reliable, because methods of analysis were used which have more recently been shown to be inaccurate, and in some cases the excretion of nitrogen had not reached a constant level at the time the temperature was artificially raised.

Simanowsky (36) raised the temperature of a bull-dog for an hour, and found, as a result, no increase in the nitrogen excretion.

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Richter (32) heated a dog for twenty-four hours, and found an increase in the nitrogen output, which chiefly took place on the day after the rise of temperature.

Formanek (8), working on man, observed a rise in the nitrogen excretion on the two days following a series of hot baths, which had raised the mouth temperature to about 102·2° F. (39° C.) or 104° F. (40° C.).

Bornstein (3), experimenting on himself, found that after raising the mouth temperature for a short time to 102·2° F. (39° C.) on two successive days, an increase in the nitrogen excretion did not occur.

F. Voit (40) found that an increase in the nitrogen output took place in dogs and rabbits. When the dogs were well fed the increase obtained was a smaller percentage of the nitrogen output for the previous period, than when the dogs were starving. No rise occurred when an excess of carbohydrate food was given. A much smaller rise took place, if the high temperature lasted only three hours instead of twenty-four hours.

Linser and Schmid (19), working on man, found that no increase in the nitrogen output took place, as long as the temperature did not rise above 102°·2 F. (39°C.). But if the temperature rose considerably above 102·2° F. (39° C.), a rise always took place. They did not find that carbohydrates entirely prevented this rise.

Description of Experiments.

The importance of this question, in the correct understanding of the metabolism of fever, led us, at Professor Fr. von Müller's suggestion, to a reinvestigation of the subject. As it was possible that the store of available carbohydrates in the body might modify the effect of high temperature on the protein metabolism in the same way, as May (24) showed was the case in fever, our experiments were arranged to study the effect of the presence or absence of carbohydrates on the changes set up by an artificially produced high temperature. In two experiments, a diet very rich in carbohydrates, but very poor in proteins, was given. The effect of this diet on the general metabolism was to reduce the daily nitrogen output to a small amount, which represented only the daily 'wear and tear' (Abnützungsquotient) of the body (Rubner (33)). Two experiments were then performed in order to test the effect of the absence of carbohydrates. In one, an ample diet was taken, which contained an excessive amount of protein and practically no carbohydrate. As the body was gaining nitrogen, a rise in the nitrogen output could not have been ascribed with certainty to the break-down of body proteins. In the other experiment, a diet of insufficient calorie value was taken, which, however, contained a moderate amount of protein and practically no carbohydrate. This semi-starvation diet caused a considerable loss of nitrogen, and a sudden rise in the nitrogen excretion would, presumably, have been caused by a break-down in the body proteins. If the high temperature caused a rise in the nitrogen excretion when an excessive

amount of carbohydrate was available, it would be necessary to ascribe the effect to a specific action of the high temperature. If, on the other hand, a rise only took place in the absence of carbohydrates, it would be due to an extra break-down of proteins, which would, in this case, be required to take a share in supplying fuel for the increased energy production, caused by the high temperature.

In order to avoid the usual sources of error as regards food and the collection of urine, these experiments were all made upon ourselves—two healthy adults aged 30 and 28 respectively. Exactly the same amount of the prescribed diet was eaten every day. The high temperature was produced when the nitrogen output had become constant, and the experiment was continued for two to three days afterwards, so that any delayed effects of the high temperature should not be missed. Throughout the experiments, the routine laboratory work was performed, and the daily life was kept as regular as possible.

In an investigation of the effect of high temperature on metabolism, for the purpose of applying the results to fever, it is important to copy as far as possible actual febrile conditions. Hot-air baths have often been employed to raise the body temperature in man. Owing to the physical regulation by means of sweat evaporation, fairly high external temperatures must be employed before a rise is obtained; and the result is that the skin temperature may be much above the body temperature, a state of affairs that never occurs in fever. Another disadvantage is that the rise of body temperature can only be of short duration. In these experiments, we have employed the steam-bath, which Haldane (11) among others has shown to be the most satisfactory method of maintaining a rise of temperature for any length of time. The principle involved is, that when the air is saturated with moisture, the sweat is unable to evaporate, and thus the physical method of temperature regulation is abolished. The rise of body temperature is dependent on the height of the wet-bulb thermometer, but is independent of the temperature registered by the dry-bulb thermometer. Under these conditions, an increase of the heat production takes place, for Sutton (38) has shown that a rise of body temperature is accompanied by an increase in the respiratory exchange. By regulating the amount of steam, the heat loss can be increased or diminished, with the result that a high body temperature can be kept fairly constant for any length of time. In this manner a close resemblance to fever is produced, for while the production of heat is increased, the loss of heat from the surface of the body is diminished, and the skin temperature still remains several degrees lower than the body temperature.

The steam-bath consisted of a small room provided with couches, on which it was possible to lie quite comfortably. It was heated entirely by steam, and by regulating the amount any desirable temperature could be maintained with great constancy. The bath usually began at 9 a.m. and lasted till about 2 p.m. The temperatures of the rectum and mouth were taken at frequent intervals during the bath. A dry-bulb and a wet-bulb thermometer were arranged on the couch close at hand. It was found that at a temperature of 96·8° F. (36° C.) the

readings of the two thermometers were sometimes identical, showing that the atmosphere was saturated with moisture. On shutting off the steam, the wet-bulb reading diminished more rapidly than the dry-bulb.

All the thermometers used were previously compared with a standard thermometer from the Physikalische Reichsanstalt at Charlottenburg. Two two-minute clinical thermometers were used, but for safety four or five minutes was always allowed before the readings were taken.

TABLE I. *Experiment II.*

Time.	Rectal Temperature.		Mouth Temperature.		Pulse per min.	Respirations per min.	Room Temperature.	
	°F.	°C.	°F.	°C.			Dry Bulb. °C.	Wet Bulb. °C.
9·0	99·2	37·35	97·1	36·2	—	—	—	—
9·20	99·3	37·4	99·8	37·7	—	—	37·0	35·8
9·50	99·9	37·75	99·45	37·5	—	—	37·5	36·2
10·20	100·2	37·9	100·0	37·8	—	—	37·0	36·2
10·50	101·2	38·45	101·1	38·4	—	—	37·0	36·2
11·20	102·1	38·95	102·0	38·9	104	—	37·5	37·0
11·40	103·15	39·5	103·0	39·45	123	—	37·5	37·0
12·10	104·1	40·01	103·8	39·92	120	—	38·0	37·0
12·30	104·3	40·2	103·6	39·8	128	44	32·0	33·0 ?
12·40	104·1	40·1	103·5	39·75	120	—	34·0	32·0
12·50	104·01	40·02	103·4	39·68	—	—	35·0	34·0
1·10	104·2	40·18	102·7	39·3	128	—	34·0	32·5
1·30	103·9	39·95	103·1	39·51	—	—	33·5	30·5
1·45	103·8	39·85	103·1	39·48	120	—	30·5	30·0
2·0	103·4	39·72	103·1	39·5	114	—	35·5	34·0
3·0	99·8	37·7	98·9	37·17	—	—	—	—

Table I shows the temperatures obtained during Experiment II, and is appended as an example of the observations taken. It was always found that the rectal temperature rose slowly soon after entering the bath, while the mouth temperature showed a rapid rise from the beginning. When the two readings were nearly the same, both temperatures rose steadily at the same rate. During this period, the mouth temperature was from 0·18° F. to 0·54° F. (0·1° C.–0·3° C.) lower than the rectal temperature. On two occasions, the mouth temperature was found to be a little higher than the rectal temperature. As soon as the steam was diminished the mouth temperature at once fell, owing to the cooling of the air of the bath. This irregularity in the mouth temperature has been described by Pembrey and Nicol (31) and Haldane (11); and, in this kind of experiment, it is only the rectal temperature that gives the true index of the body temperature.

Linser and Schmid (19) heated their patients by means of a Phoenix hot-air bath to temperatures of about 104° F. (40° C.). The temperature of the bath was 109·4° F. (43° C.); the patients lay in the bath with the head projecting into the air of the room, and only mouth temperatures were taken.[1] In one case

[1] We wish to thank Professor Linser for kindly supplying us with information on this point.

a temperature of 104·7° F. (40·4° C.) was obtained in three-quarters of an hour. At lower temperatures, i. e. in a room at 96·8° F. (36° C.), they found an average difference between mouth and rectal temperatures of 0·9° F. (0·5° C.). It might be inferred that in these experiments with the Phoenix bath, the rectal temperatures were at least 0·9° F. (0·5° C.) higher than the observed mouth temperatures, because the head and mouth were outside the bath. This point was of considerable importance to us, as if this was the case, the rectal temperatures at which a rise in the nitrogen excretion occurred would be usually somewhat above the temperatures that we were able to reach in our experiments. We have investigated the matter further by means of an electric light bath, in which the patient lies at full length. Although the head projected into the room, the heat that escaped from the bath, together with the heat of the face and clothes, caused the mouth and rectal temperatures to be practically identical; the greatest difference observed was 0·1° F. (0·06° C.), and on many occasions the mouth temperature was either equal to or a little above the rectal temperature. This latter occurrence takes place when the temperature of the surrounding air is above the body temperature (Haldane (11)). In order to take readings of the rectal temperature, the thermometer was handed out from the bath by means of a small movable window. There was the possibility that the readings might be vitiated by the heat of the bath during this process, although the time required for it was three seconds at the outside. Experiment showed that, under these conditions, it required 1 min. 25 sec. for the mercury to begin to rise, if the thermometer was held inside the bath. From these results, it must be concluded that the rectal temperatures of Linser and Schmid's patients while in the Phoenix bath were practically identical with, and sometimes a little below, the mouth temperatures which they observed.

The rise of body temperature in the steam-bath always produced some definite symptoms. It was possible to lie still and read a novel in comparative comfort, until a body temperature of 102·2° F. (39° C.) had been reached. Above this temperature, restlessness and irritability became gradually noticeable. The greatest discomfort was produced by the oppressiveness of the atmosphere of the bath; the sweat evaporation was prevented, and the skin temperature rose in consequence. If the steam were diminished, this feeling disappeared, although the rectal temperature remained for a while as high as before, and sometimes continued to rise. An additional cause of distress, in the case of G. G., was dyspnoea, which was noticed particularly in Experiment II with a body temperature above 104° F. (40° C.), but this symptom was relieved on reduction of the room temperature. In Experiment II and in Experiment III (second bath), the general discomfort was so great, that it was found impossible to eat the midday meal, which was usually taken during the bath. Frequency and precipitancy of micturition were always observed in the case of G. G., and the volume of urine passed was always greater during the bath than for the corresponding period on other days. In the case of E. P. P., precipitancy of micturition and some frequency were noticed on both occasions in Experiment III,

but the actual volume of urine passed was no greater than usual. In Experiment I no urine at all was passed during the bath, and no water was taken by the mouth, and the volume for this period was much less than usual. A sensation of pins and needles in the hands was observed by E. P. P. in Experiment III on the second temperature day (temperature 102·9° F. (39·4° C.)). It became very unpleasant, and was only partially alleviated by dipping the hands in a basin of cold water. This sensation is very easily produced in this subject by means of forced breathing (Haldane and Poulton (12)). In the case of E. P. P., the pulse-rate was very susceptible to a rise of temperature. On both temperature days in Experiment III the pulse was 120 or more by the time the rectal temperature had reached 100·4° F. (38° C.). On the first 'temperature' day, the pulse remained over 140 most of the time, and actually reached 152. On the other hand, during the greater part of the bath E. P. P.'s respiration rate was low, being 12 per minute; it only rose to 20 when the rectal temperature was in the neighbourhood of 104° F. (40° C.). The reverse was noticed in the case of G. G. The respiratory rate showed a greater tendency to rise, while the pulse frequency reached 120 only when the rectal temperature was about 103·1° F. (39·5° C.). When the temperature rose to 104·4° F. (40·2° C.), in Experiment II., the respirations were actually 44 per minute, while the pulse was 128. In Experiment IV with a rectal temperature of 103·3° F. (39·6° C.) the respirations were 36, the pulse 130 per minute.

After the bath, considerable limpness was experienced, but there was no feeling of faintness. A douche was given, and an hour's rest in bed was always taken. A disagreeable headache was invariably noticed, and there was a feeling of slackness during the rest of the day, and often during the next day as well. E. P. P. noticed a little giddiness. The midday meal was taken during the bath, and water was given when desired. The effect of these two factors was, on three occasions, to produce a gain of weight at the end of the bath. On the first temperature day, Experiment III, E. P. P. actually showed an increase in weight of 1·9 kilos after the bath, and at the same time some oedema of the face was noticed.

Our symptoms at the beginning of the bath were much less marked than those described by Sutton (38) under somewhat similar conditions.

Methods of Analysis.

The total nitrogen was estimated by Kjeldahl's method. In all the experiments, the urine was collected separately in fractions for three periods in the twenty-four hours. The total nitrogen in each fraction was estimated. In Experiments II, III, and IV the periods were eight hours each. In Experiment I, two of the periods were six hours in length, the third period was twelve hours. The volumes of the fractions were measured separately, and exactly one-tenth was withdrawn from each for the nitrogen determinations. The remaining nine-tenths of the fractions were mixed together for the other determinations. In cases where the urine was very concentrated, it was sometimes necessary, in

the first place, to dilute the fractions with water to a known volume, and one-tenth of this volume was then removed. In addition to estimating the nitrogen of each fraction, the nitrogen for the whole twenty-four hours was also estimated. The two values for the total nitrogen so obtained usually agreed within 1 per cent. All these analyses were performed in duplicate, and the same was the case with the other determinations mentioned in this paper, except the β-oxybutyric acid and creatinine.

Kjeldahl's method was employed for the determinations of the nitrogen in the food, sweat, and faeces. The calorie values were obtained by consulting Atwater and Bryant's tables (2), but in some cases Koenig's *Chemie der Nahrungs- und Genussmittel* was also consulted.[2]

The amount of ammonia was estimated in Experiment II by Schaffer's method, and in Experiments III and IV by Folin's method. In each case the apparatus was tested by means of an ammonia solution of known strength.

The urea was determined by the Mörner-Folin method (25). A slight modification, based on Spiro's method (37), was introduced to shorten the process. The urine (10 c.c.) was measured into a 200 c.c. flask with a graduated neck, and 5 grammes of barium hydrate were added. After saturation had taken place, the alcohol and ether mixture was poured in, and the whole shaken. The flask was allowed to stand overnight in a vessel of tap-water. In the morning the volume was read off on the graduated neck, and some of the liquid was poured rapidly through a folded filter-paper into a 100 c.c. measuring flask kept at the same temperature. A definite fraction of the urea was in this way obtained. This procedure takes much less time than the original method, where the precipitate must be filtered off and thoroughly washed. The actual volume of the precipitate in the 200 c.c. flask was found to be negligible.

The uric acid was determined by the Ludwig-Salkowski method; Kjeldahl's method was used for the final stage.

The creatinine was determined by Folin's method, an Autenrieth-Königsberger colorimeter being used. In Experiment IV, a modification was made in the method because acetone was being excreted in the urine. The urine (50 c.c.) was mixed with 5 c.c. of a 10 per cent. phosphoric acid solution in a 100 c.c. flask, and then distilled for one and a half hours *in vacuo* at a temperature of 40–45°C. The solution was then cooled and diluted to 100 c.c., and the estimation made in the usual way. By this method the acetone was almost completely distilled off, although the solution still gave a faint nitro-prusside reaction (Rothera's method).

In every case, a creatine estimation was made by Folin's method, but in no case was any creatine detected.

The acetone was estimated by a modification of the Messinger Huppert method; only one distillation was made, and 10 per cent. phosphoric acid was used.

The β-oxybutyric acid was estimated by the polarimeter method. A Magnus Levy ether extraction apparatus was used, and the urine was continuously extracted for forty-eight hours, and then for a further twenty-four hours, to make certain that the first extraction was complete. As it was impossible to estimate the β-oxybutyric acid at the same time as the other estimations, the exact quantity of urine required (170 c.c.) was preserved under ether in a corked bottle and analysed later. The β-oxybutyric acid has been repeatedly found by O. Neubauer to undergo no decomposition under these conditions.

Carmine powders were used for separating the faeces into different periods.

[2] The amount of fat in the cream was determined by the Schmidt Werner method in order to calculate the calorie value.

Analysis of Sweat.

In all the experiments except Experiment I, the nitrogen in the sweat during the bath was determined.

A preliminary scrubbing with soap and water served to remove all loose scales of epidermis from the skin.

The sweat was collected by means of an indiarubber bath, in which the subject lay. The legs and the upper parts of the body were covered with one layer of clothes, which had previously been rendered nitrogen free by boiling with water, after having been soaked in a $\frac{1}{10}$ per cent. oxalic acid solution. At the end of the bath, the skin was carefully rinsed down with water and the washings were collected in the indiarubber bath. The clothes were soaked in weak oxalic acid, and were then boiled twice in water. All the washings were mixed together, and their volume measured; the total nitrogen was then estimated. In order to estimate the urea and ammonia in the sweat, a known volume of the washings was evaporated down to dryness with hydrochloric acid on the water-bath, and subsequently heated with magnesium chloride and hydrochloric acid, and proceeded with as in the Mörner-Folin method. In Experiment II the indiarubber bath was not used, but the sweat was collected by means of two layers of clothes. For comparison, the quantity of nitrogen excreted normally in the sweat was estimated. The subject E. P. P. wore the same vest, shirt, and drawers day and night for forty-eight hours, during Experiment III. The clothes were then treated as previously described. The nitrogen was estimated and also the urea and ammonia. The values are too low, as the sweat was not collected from the skin of the face, the scalp, the forearm, or from the legs below the knees.

TABLE II.

Analysis of Sweat.

	Experiment II. Temperature Day.	Experiment III. 1st Temperature Day.	Experiment III. 2nd Temperature Day.	Experiment III. Sweat collected for a 48-hourly period.	Experiment IV. Temperature Day.
Total nitrogen .	0·201 grm.	0·803 grm.	0·562 grm.	0·572 grm.	0·536 grm.
The urea and ammonia of sweat in grm. of nitrogen	0·102* „	0·356† „	0·249 „	0·446 „	0·272 „
Percentage of urea and ammonia to total nitrogen . . .	50·7 %*	44·3 %†	44·3 %	78·0 %	50·7 %

* Calculated, assuming that the proportions of urea and ammonia to total nitrogen were the same as in Experiment IV.

† Calculated, assuming that the proportions of urea and ammonia to total nitrogen were the same as on the second 'temperature' day of Experiment III.

The urea and ammonia formed 78 per cent. of the total nitrogen when the sweat was collected in Experiment III during the 48-hourly period. The remaining 22 per cent. must have been chiefly due to epidermal scales, hairs, and débris rubbed off on the clothes, and in less amount to uric acid and other nitrogen-containing bodies (Camerer (4)). On the second temperature day (Experiment III), 55·7 per cent. of the total nitrogen in the sweat was accounted for in this way. This large percentage must have been due to the soddenness of the skin, as a result of the bath, and a large number of the superficial scales must

have been loosened and included in the sweat. In Experiment IV, this percentage was 49·3, as particular care was taken to rub the skin as little as possible in the collection of the sweat at the end of the experiment, and it is probable that fewer epidermal scales were rubbed off from the skin. The question arises, whether the sweat nitrogen should be added to the total nitrogen for the 'temperature' day, when the nitrogen output for this day is compared with that for the other days of the experiments.

It is obvious that the loss of nitrogen due to the epithelial débris must not be added, as compensation for this sudden loss of nitrogen would be spread over several days. On the other hand, it seems possible that the loss of urea and ammonia in the sweat would be compensated for on the day itself by a diminution in the urinary excretion. If this were the case, the urea and ammonia should be added to the total nitrogen to get the balance for the day. It will be seen that in Experiment III 0·223 grm. of urea and ammonia was excreted normally in twenty-four hours in the sweat. On the second temperature day (Experiment III), 0·249 grm. was excreted during the period of four hours, in which the bath was being taken. It is difficult to say whether or not this latter excretion would cause an increase or diminution of the normal excretion during the rest of the day. However, this consideration has been neglected, and in each case the urea and ammonia nitrogen in the sweat has been added to the nitrogen in the urine to get the nitrogen balance for the day.

Experiment I. (Subject E. P. P.)

The daily diet was as follows:

Food-stuff.	Amount.	Nitrogen.	Calories.
Arrowroot	500 grm.	—	2050
Cream	306 „	1·23 grm.	1350
Lactose	200 „	—	775
Cane sugar	80 „	—	320
Juice of 1 lemon			
Tea	400 c.c.	neglected	
Salt	6 grm.		
	Total	1·23 grm.	4495

Weight during experiment, 72·4 kilos.

Calories per kilo at beginning of experiment = 62·0.

After the experiment had started, it was felt that it would be more satisfactory if the calorie value of the diet was increased. Consequently on the fifth and sixth days of the experiment about 60 grm. of butter (i.e. 451 calories) were added to the diet, so that on these days the calorie value of the food was 68·0 calories per kilo. On the last four days of the experiment about 150 grm. of butter were added to the diet each day. The addition of the butter was found not to alter appreciably the nitrogen content of the food.

The arrowroot was partially digested with diastase in the manner described by Folin (7), and the salt was stirred into the mixture, which was eaten with cream and sugar. The lactose was taken with lemonade.

The effect of the diet was to produce some digestive disturbance, as evidenced by the breath becoming unpleasant, especially before meals. A furred tongue was noticed on the fourth day, and there was a sweetish taste in the mouth. After a week it was noticed that laboratory work was performed more slowly than usual. A certain amount of giddiness was felt.

No albumen, sugar, acetone, or diacetic acid were at any time detected in the urine.

The steam-bath was taken on the eighth day of the experiment. A rectal temperature of 102·7° F. (39·3° C.) was reached within one hour from the beginning, the wet bulb being 96·8° F. (36° C.). The body temperature was then allowed to fall, and was kept at about 101·3° F. (38·5° C.) for most of the rest of the experiment. The rectal temperature was above 100·4° F. (38° C.) for 3¾ hours. Such a rise of temperature, though not very high, was such as often occurs in many febrile conditions.

TABLE III. *Experiment I.* (Subject E. P. P.)

Date, Jan. 9–17, 1912. Amount of nitrogen in food = 1·23 grm. per diem.

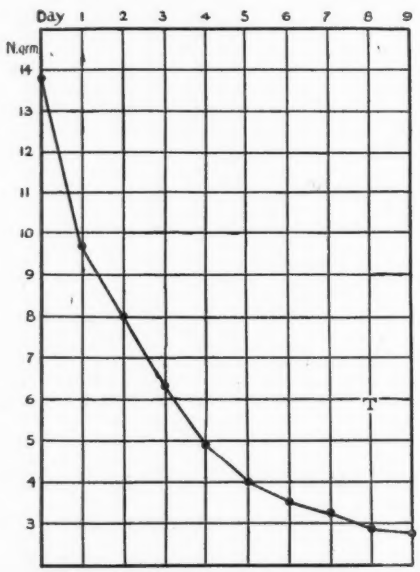
Day of Expt. and Weight in Kilos.	Vol. in c.c.	Total N. grm.	Urea. Grm. of N.	Urea. % of total N.	Uric Acid. Grm.	Uric Acid. Grm. of N.	Uric Acid. % of total N.	Creatinine. Grm.	Creatinine. Grm. of N.	Creatinine. % of total N.	Faeces. Grm. of N.	N. Balance. Grm. of N.
0 72·6	1460	13·89	11·6	83·5 %	0·591	0·197	1·42 %	—	—	—	—	—
1	730	9·713	7·81	80·4 %	0·447	0·149	1·53 %	1·708	0·635	6·53 %	1·12	−9·60
2	1350	8·032	6·37	79·3 %	0·357	0·119	1·48 %	—	—	—	1·12	−7·92
3	1405	6·300	4·56	72·4 %	0·354	0·118	1·87 %	2·214	0·823	13·1 %	1·12	−6·19
4 72·4	1298	4·967	3·34	67·2 %	0·345	0·115	2·31 %	1·985	0·738	14·85%	1·12	−4·86
5	1440	4·150	2·42	58·3 %	0·297	0·099	2·39 %	2·077	0·772	18·6 %	1·21	−4·13
6	1087	3·633	2·10	57·8 %	0·306	0·102	2·81 %	2·033	0·755	20·8 %	1·21	−3·61
7	1338	3·39	1·97	58·1 %	0·312	0·104	3·07 %	2·087	0·776	22·9 %	1·21	−3·37
												−39·68
8* 72·4[1] 71·9[2]	1215	2·90	1·46	50·35%	0·249	0·083	2·86 %	1·974	0·734	25·3 %	1·21	−2·88
9	1095	2·869	1·69	58·9 %	0·252	0·084	2·93 %	2·040	0·758	26·4 %	1·21	−2·85
												−45·41

* Steam-bath taken on this day. [1] Before bath. [2] After bath.

It will be observed from Table III and from the curve in Diagram 1, showing the daily nitrogen excretion, that this fell steadily throughout the experiment. On the first day it fell from 13·89 to 9·713 grm. On the seventh day the excretion was 3·39 grm.; on the eighth day, which was the 'temperature' day, the nitrogen excretion was 2·90 grm.; and on the following day it was 2·87 grm. From the curve it appears that the nitrogen excretion was still falling when the bath was taken, although it had nearly reached a constant level. The amounts of nitrogen excreted on the 'temperature' day and on the day following occupy positions on the curve, that agree with the steady diminution in the nitrogen output from day to day. The conclusion is that the high temperature produced no rise in the nitrogen excretion on these days. If anything, slightly less nitrogen was excreted on the day of the bath, but this

may have been due to the nitrogen in the sweat; in this experiment no analysis of the sweat was made.

The amount of nitrogen which was excreted in the form of urea, uric acid, and creatinine, was determined throughout the experiment, and is shown in Table III. The diet used in this experiment and in Experiment II contained a very small quantity of nitrogen, but was of high calorie value, and the changes produced by the diet on the nitrogen distribution in both these experiments agree with Folin's observations with a similar diet (7). The amount of urea nitrogen fell from day to day, and at the same time its percentage of the total nitrogen also fell from 80·4 per cent. to 58·1 per cent. on the seventh day of the diet. On the eighth day, the day of the bath, the percentage of urea nitrogen dropped to 50·35 per cent., but rose again on the



EXPERIMENT I. DIAGRAM 1. The points on the curve show the total nitrogen in grammes excreted in the urine on each day. T represents 'temperature' day.

following day to 58·9 per cent. This diminution on the 'temperature' day was probably due to an increase in the formation of ammonia, as this was found to be the case in Experiment II, and the explanation will be discussed later.

The uric acid nitrogen gradually fell as the result of the diet, while its percentage of the total nitrogen rose. The bath produced no alteration in this excretion.

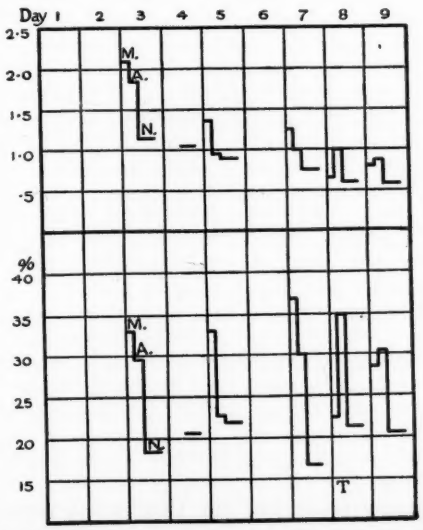
The excretion of creatinine showed some fluctuations on the first and third days of the experiment, but during the last six days it was extremely constant, varying between 1·985 grm. and 2·087 grm. Its percentage of the total nitrogen rose from 6·53 per cent. to 26·4 per cent. The high temperature did not produce any alteration in the excretion.

The method of collecting and analysing the urine in fractions, in order to study the diurnal variations in the nitrogen excretion, has already been described. The object of this investigation was to discover, in the event of the high temperature causing a rise in the nitrogen output, the exact period during which the increase took place. Though no rise in the nitrogen output occurred,

TABLE IV. *Experiment I. Fractions.*

Day of Expt.	Morning Period. 8 a.m.–2 p.m.			Afternoon Period. 2 p.m.–8 p.m.			Night Period. 8 p.m.–8 a.m.			Total N., i.e. sum of fractions.
	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	
3	437	2·08	33·1 %	578	1·86	29·7 %	390	2·33	37·2 %	6·27
4	575	2·98	59·0 %	Morning and afternoon fractions analysed *en masse*			723	2·06	40·8 %	5·05
5	497	1·38	33·2 %	155	0·95	22·8 %	788	1·83	43·9 %	4·16
6	Errors in the collection of the fractions on this day.									
7	613	1·25	37·2 %	490	1·00	29·8 %	235	1·11	33·0 %	3·36
8*	160	0·65	22·4 %	292	1·02	35·0 %	375	1·24	42·6 %	2·91
9	167	0·80	28·2 %	531	0·87	30·6 %	518	1·17	41·2 %	2·84

* Bath taken on this day.



EXPERIMENT I. DIAGRAM 2. The upper series of figures show the amount of nitrogen, in grammes per 6 hours, excreted in the urine during the following periods of the day: 8 a.m.–2 p.m., 2 p.m.–8 p.m., 8 p.m.–8 a.m. The lower series of figures represent the percentage amounts of the total nitrogen which were excreted during each period of the day. (T represents 'temperature' day.)

the results of the investigation are given as being of some interest. Table IV shows the results obtained, and the amount of nitrogen excreted is further shown by the upper series of figures in Diagram 2. Each figure corresponds to one day's excretion, and in each case the line M represents the nitrogen output during the six-hourly period from 8 a.m. to 2 p.m.; A represents the afternoon

excretion, and N represents the excretion during the twelve-hourly period from 8 p.m. to 8 a.m. Each figure thus represents a day's excretion divided into four periods of six hours each. Throughout the experiment, the total amount of nitrogen passed in the twelve-hourly period during the night, from 8 p.m. to 8 a.m., was always less than that passed during the day, from 8 a.m. to 8 p.m. This agrees with what Landergren (17) found on a similar diet. However, in order to compare the amounts of nitrogen excreted for the two separate six-hourly periods of the day with the night's excretion, it is necessary to halve the value of the latter, as the period was of twelve hours' duration, and in this way the figures in Diagram 2 have been constructed.

It will be seen that the largest excretion of nitrogen took place during the morning period, on all the days preceding the bath.

On the fourth day, owing to a mistake in the collection of the urine, the amount passed from 8 a.m. to 8 p.m. was analysed *en masse*, instead of being collected into two fractions of six hours each, and so only the night's excretion can be used for purposes of comparison on this day. As the total nitrogen excretion for the day was diminishing throughout the experiment, the actual amounts excreted during the corresponding periods on different days also diminished. Thus, on the third day the morning's excretion was 2·08 grm.; on the fifth day it was 1·38 grm.; and on the seventh day it was 1·25 grm. This diminution makes it difficult to compare the fractions of one day with the corresponding fractions of another for the purpose of detecting any irregularities. We have therefore calculated what percentage of the total nitrogen for the day was excreted during each period (Diagram 2, Table IV). If the same percentage amounts of the total nitrogen output for the day were always excreted for corresponding periods, the percentage curves in the diagram would be similar to one another; but this, as will be seen, was not the case. The percentages for the morning periods before the bath vary from 33·1 per cent. to 37·2 per cent., and for the afternoon periods from 22·8 per cent. to 29·8 per cent., and for each six-hourly period during the night from 16·5 per cent. to 21·9 per cent.

A still greater variation was observed on the day of the bath (eighth day). The nitrogen excretion for the morning period, during which the bath was taken, was very much diminished, being only 22·4 per cent. of the total excretion for the day, i.e. 12 per cent. lower than the average percentage for the morning period of the preceding days. In the afternoon the output was increased, the percentage being 35·0 per cent., i.e. 7·6 per cent. above the average. The night's excretion remained about the same as usual. The volume of the urine passed during the morning, when the bath was taken, was 160 c.c., and this was much less than usual. No frequency or precipitancy of micturition was noticed. On the other hand, sweating was considerable, and no water was taken to drink during the bath. The loss of body weight during the bath was 0·5 kilo.

The most probable explanation is that the diminished nitrogen output on the morning of the 'temperature' day was the result of the smaller volume of urine passed, and that later, during the afternoon, this temporarily retained nitrogen was washed out.

It seems a definitely recognized fact that, under ordinary conditions, the total amount of nitrogen excreted for the day is not influenced by the volume of urine secreted. Even after severe exercise the volume of urine may be diminished, though the nitrogen excretion is increased (Dunlop and others (6)). However, Abderhalden and Bloch (1) have shown that a slight increase of nitrogen is obtained, on drinking a very large quantity of water; and they believe that this is due to the washing out of non-protein nitrogenous substances from the body. In our experiments the amount of water taken by the mouth was about the same each day, although it was not accurately measured; and so there is no possibility of the total nitrogen output for the day being affected by this washing-out process. On the other hand, there are several indications in this

experiment that the volume of urine secreted did influence the rate of nitrogen excretion through the day. The variations in the percentages noted above may be explained on this hypothesis. Before the 'temperature' day, the largest volume of urine was excreted during the morning period, except on the third day, and the greatest amount of nitrogen was always excreted during this period. On the afternoon of the fifth day, the percentage amount of nitrogen excreted was much lower than usual, viz. 22·8 per cent., and during this period the volume was only 155 c.c. On the morning after the bath, the volume was again only 167 c.c., and the percentage amount of nitrogen excreted was also diminished. It does not appear that the excretion of a large volume of urine necessarily caused a larger excretion of nitrogen than usual; for in some cases the excretion of nitrogen was less than usual under these conditions.

However, there does seem to have been a definite rule that, when the volume of urine was low, the percentage amount of nitrogen excreted for the same period was also lower than usual. The fractions in Experiments II and IV also agree with this rule. This fact cannot be due to the inability of the kidneys to pass urine of more than a certain concentration, because, if the amount of nitrogen excreted is calculated per c.c. of the volume, the highest concentration obtained in this experiment is much less than that found in Experiment III.

It seems reasonable to believe that a certain rate of flow of water through the kidneys is necessary in order to keep the excretion of nitrogen for any particular period up to the normal level.

As the greatly diminished urinary volume on the morning of the 'temperature' day was due to the profuse sweating, and the diminution for the same period on the next day might have been also due to disturbances set up by the same cause, the alterations in the distribution of the nitrogen output on these days might be said to be an indirect effect of the high temperature.

Experiment II. (Subject G. G.)

The constant daily diet taken is shown in the following table:

Arrowroot . .	470 grm.	0 grm. N.	1927 cal.
Biscuits . . .	240 „	0 „ „	984 „
Lactose . . .	200 „	0 „ „	775 „
Cream	228 „	0·912 „ „	1000 „
Salt	10 „	—	—
		0·912 grm. N.	4686 cal.

Calories per kilo at the beginning of the experiment = 75·1.

Calories per kilo at the end of the experiment . . = 76·4.

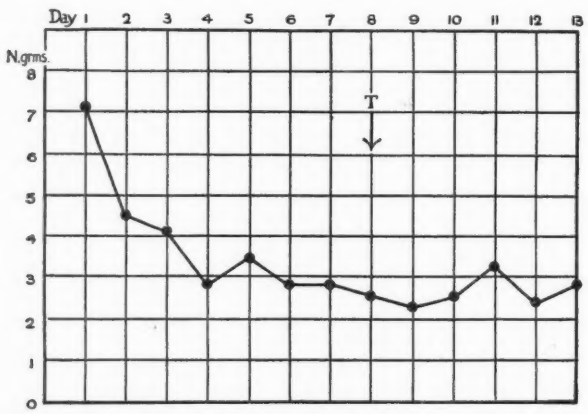
The arrowroot was divided into three portions, and eaten with lactose, salt, and cream; about 80 grm. of the nitrogen-free biscuits described by Thomas (39) were added to each meal. After the first two meals the diet seemed satisfying, and caused practically no inconvenience. No difficulty was found in doing the usual laboratory work until after the temperature day, when the necessity of catching up some arrears of work caused more fatigue than usual. On the eleventh and thirteenth days a new and much stronger brand of diastase was accidentally supplied, with the result that the preliminary digestion of the arrowroot was carried much too far, and the food was exceedingly

nauseous. On both these days, but particularly on the thirteenth day, considerable discomfort was felt, and the work was very irksome.

The return to the ordinary diet relieved all the digestive symptoms, and three days later a twelve-hour tour was made in the mountains without undue fatigue. The body weight increased by 0·2 kilo during the first eight days; it decreased by 1 kilo on the temperature day and by 0·5 kilo during the last three days. The net loss was 1·3 kilos.

The temperature was produced on the eighth day. A rectal temperature of 102·2° F. (39° C.) was reached after 2 hours 20 minutes, and 104·27° F. (40·2° C.), R. 44, P. 128, after $3\frac{1}{2}$ hours. A temperature over 102·2° F. (39° C.) was maintained for $2\frac{1}{2}$ hours, and over 104° F. (40° C.) for $1\frac{1}{4}$ hours. Considerable distress was felt when this temperature was first reached, but the unpleasant symptoms soon passed off after the reduction of the room temperature, although the body temperature remained above 104° F. (40° C.).

No sugar, albumen, or acetone were detected in the urine on any occasion.



EXPERIMENT II. DIAGRAM 3. The points on the curve show the total nitrogen in grammes excreted in the urine on each day.

The total nitrogen excreted in the urine on an ordinary mixed diet before the experiment began was 12·11 grm. The effect of the carbohydrate diet on the nitrogen output (Table V, Diagram 3) was to produce a rapid fall to 2·868 grm. on the fourth day. A slight rise occurred on the fifth day, but was followed by a fall to 2·789 grm. on the sixth day. On the eighth or temperature day the nitrogen output fell to 2·564 grm., and reached its lowest point on the first day after the bath, when 2·25 grm. were excreted. A slight rise occurred on the second day after the bath, and was followed by a marked rise on the third day.

The high temperature did not cause any increase in the nitrogen output; in fact, the total nitrogen output was diminished on the temperature and two succeeding days. Even if the whole amount of the nitrogen excreted in the sweat, 0·201 grm., instead of the estimated value for the urea and ammonia

TABLE V. *Experiment II. Date, Jan. 31–Feb. 15, 1912.*

Day of Expt. Weight in kilos.	Vol. in c.c.	Total N. Grm.	Urea. Grm. of N.	Urea. % of total N.	Ammonia. Grm. of N.	Ammonia. % of total N.	Urea and Ammonia. Grm. of N.	Urea and Ammonia. % of total N.	Uric Acid. Grm.	Uric Acid. Grm. of N.	Uric Acid. % of total N.	Creatinine. Grm.	Creatinine. Grm. of N.	Creatinine. % of total N.	Undetermined Nitrogen. Grm. of N.	Undetermined Nitrogen. % of total N.	Faeces. Grm. of N.	Nitrogen Balance. Grm. of N.
0	2020	12·11	—	—	0·521	4·30%	—	—	0·402	0·134	1·11%	—	—	—	—	—	—	—
1 } 62·4	1846	7·148	5·31	74·29%	0·356	4·98%	5·666	79·27%	0·348	0·116	1·62%	—	—	—	—	—	1·020	−7·256
2	1033	4·578	—	—	—	—	—	—	0·282	0·094	2·05%	1·553	0·576	12·58%	—	—	1·020	−4·686
3	2313	4·152	2·865	69%	0·403	9·71%	3·268	78·71%	0·252	0·084	2·0%	1·553	0·576	13·87%	0·224	5·4%	1·131	−4·371
4	1074	2·868	1·72	60·19%	0·270	9·41%	1·99	69·6%	0·264	0·088	3·1%	1·577	0·585	20·4%	0·2	6·97%	1·131	−3·087
5	1537	3·369	2·044	60·81%	0·314	9·32%	2·358	70·13%	0·237	0·079	2·3%	1·685	0·625	18·55%	0·31	9·11%	1·131	−3·588
6	1538	2·789	1·49	53·42%	0·321	11·51%	1·811	64·93%	0·282	0·094	3·37%	1·69	0·627	22·48%	0·255	9·14%	1·131	−3·008
7	1662	2·779	1·602	57·65%	0·315	11·34%	1·917	68·99%	0·264	0·088	3·2%	1·563	0·58	20·87%	0·194	6·98%	1·131	−2·998
62·6[1] T 8 61·6[2]	1889	2·564	1·209	47·15%	0·397	15·48%	1·606	62·63%	0·291	0·097	3·79%	1·702	0·632	24·65%	0·229	8·93%	1·131	−2·783
9	1237	2·250	1·047	46·54%	0·343	15·25%	1·390	61·79%	0·216	0·072	3·2%	1·612	0·598	26·58%	0·190	8·44%	1·131	−2·469
10 } 61·1	1145	2·495	1·183	47·41%	0·334	13·39%	1·517	60·80%	0·291	0·097	3·89%	1·617	0·60	24·05%	0·281	11·26%	1·131	−2·714
11	1826	3·211	1·88	58·55%	0·377	11·74%	2·257	70·29%	0·336	0·112	3·48%	1·65	0·612	19·06%	0·230	7·16%	—	—
12	1178	2·348	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
13	2357	2·763	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

T Steam-bath taken on this day.

[1] Weight before bath.

[2] Weight after bath.

nitrogen, 0·102 grm., be added to the total nitrogen excreted in the urine, a slight fall is still seen. The rise which took place on the eleventh day can scarcely be attributed to a delayed effect of the high temperature, as it took place three days after the temperature day. There were two possible independent factors which might have accounted for this unexpected rise in the nitrogen output. Some intestinal disturbances were apparent early in the day since a very large semi-solid stool (dry weight 96 grm.) was passed at 8 a.m. after a little abdominal discomfort, and the last portions were liquid and coloured with the carmine powder, which had been taken only one hour before in order to separate off the stool. The intestines were, therefore, in all probability completely emptied of the remains of previous meals. In addition, the food on this day was exceedingly nauseous, but had to be eaten as there was a great scarcity of arrowroot. These two conditions seem quite sufficient to explain the rise in the nitrogen output which occurred. Some additional confirmation of this view is also obtained from the result of the thirteenth and last day of the experiment, when the food was again exceedingly nauseous, and another rise in the nitrogen output occurred.

The complete nitrogen distribution was determined, and as in Experiment I the result agrees very well with Folin's observations, although some changes occurred as a result of the high temperature.

The ammonia output on the first day of the experiment was 0·356 grm.; on the fifth day it had fallen to 0·314 grm. nitrogen, and the average for the three days preceding the high temperature was 0·317 grm. nitrogen. On the temperature day it rose to 0·397 grm. nitrogen, and on the two succeeding days it was 0·343 grm. nitrogen and 0·334 grm. nitrogen. On the third day after the bath, when the food was nauseous, it rose again to 0·377 grm. nitrogen. The rise in the ammonia output on the temperature day means that some additional acid was formed in the body, and this effect still persisted to a slight extent on the next two days. No acetone could be detected in the urine, and the nature of the acidosis remained undetermined.

The urea output was very much decreased as a result of the low nitrogen diet, and formed a much smaller percentage of the total nitrogen than usual. On the first day of the diet it was 5·31 grm., and formed 74·29 per cent. instead of about 88 per cent., which is the usual percentage with an output of about 12 grm. nitrogen; on the seventh day of the diet it was 1·602 grm., and formed 57·65 per cent. of the total nitrogen output.

On the temperature day the urea output fell to 1·209 grm. nitrogen, and formed only 47·15 per cent. of the total nitrogen output. On the day after the temperature day, when the total nitrogen output amounted only to 2·25 grm. nitrogen, the urea output was 1·047 grm. nitrogen, and formed 46·54 per cent. of the total nitrogen output; on the second day after the bath the total nitrogen output had risen to 2·495 grm. nitrogen, and the urea output rose to 1·183 grm. nitrogen and formed 47·41 per cent.; on the third day the total nitrogen output rose to 3·211 grm., and the urea consequently rose to 1·88 grm. nitrogen and formed 58·55 per cent.

The changes in the urea nitrogen output were partly due to the fall in the total nitrogen output, as Folin has shown that 'urea is the only nitrogenous substance in the urine which undergoes an absolute and relative decrease' when the total nitrogen output is reduced. But on the temperature day the fall in the urea was too great to be explained entirely in this way. The only other constituent in the urine, which is nearly related to the urea, is the ammonia, and the ammonia on this day was increased in order to neutralize some acidosis. Consequently less nitrogen was excreted in the form of urea, and more as ammonia.

The very low percentage of the urea on the first two days after the temperature day is also explained partly by the lowness of the total nitrogen output, and partly by the ammonia output, which still remained a little raised.

These results explain the fall in the urea nitrogen output which occurred in Experiment I on the temperature day, and, in the absence of any ammonia figures, was not clear. They show that in Experiment I some acidosis must also have been set up by the high temperature. The rise in the urea output on the third day after the bath is explained by the rise in the total nitrogen output occasioned by the digestive disturbances.

The uric acid output fell steadily from 0·348 grm. on the first day to 0·237 grm. on the fifth day; on the sixth day it rose to 0·282 grm. and fell to 0·264 grm. on the day before the temperature day. On the temperature day the uric acid output was 0·291 grm. or slightly higher than on the preceding day. It fell on the day after to 0·216 grm., but rose to 0·291 grm. on the second day after the bath; on the third day after the bath it rose to 0·336 grm.

The slight rise in the uric acid output on the temperature day cannot be ascribed to the effect of the high temperature, as it was not greater than the daily variations of the experiment.

The creatinine output was very constant throughout the experiment, and varied between 1·553 grm. and 1·702 grm. The highest output, 1·702 grm., occurred on the temperature day, but the output was only 0·012 grm. higher than that which had occurred two days previously, and consequently the output of a creatinine can be considered as within the normal limits of the experiment.

No creatine was detected on any occasion.

The balance of the nitrogen, which was left undetermined by the methods employed, was very constant when it is considered that it is influenced by any errors in the other estimations. It varied between 0·31 and 0·19 grm. nitrogen.

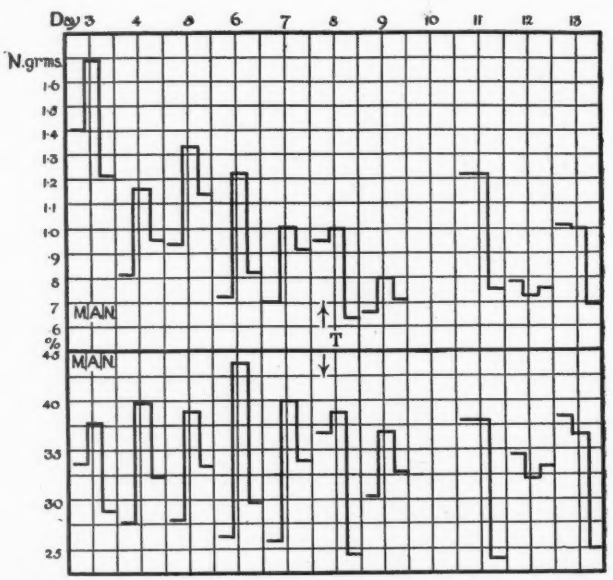
The diurnal variations in the nitrogen output are shown in Table VI and Diagram 4. In this experiment the day was divided into three equal periods, 7 a.m.–3 p.m., 3 p.m.–11 p.m., and 11 p.m.–7 a.m. The diurnal variations of nitrogen output from the third to the seventh day were very similar in character. The smallest excretion always took place during the morning and the greatest in the afternoon period. The total nitrogen output during these five days fell from 4·2 grm. nitrogen on the third day to 2·7 grm. on the seventh day, but the diminution was not spread quite evenly over the whole day. Thus the nitrogen output during the morning period formed 33·33 per cent. of the total nitrogen

output on the third day, but only 25·93 per cent. on the seventh day. A slight rise in the total nitrogen output on the fifth day was also accompanied by a slight rise in the percentage nitrogen output during the morning period. The percentage nitrogen output during the afternoon period rose from 37·86 per cent. on the third day to 40 per cent. on the seventh day, but it was not quite regular

TABLE VI. *Experiment II.*

Day of Expt.	Morning Period. 7 a.m.–3 p.m.			Afternoon Period. 3 p.m.–11 p.m.			Night Period. 11 p.m.–7 a.m.			Total N. of Periods.
	Vol. in c.c.	Grm. of N.	% of total N.	Vol. in c.c.	Grm. of N.	% of total N.	Vol. in c.c.	Grm. of N.	% of total N.	
3	436	1·40	33·33%	909	1·59	37·86%	968	1·21	28·81%	4·2
4	155	0·81	27·55%	472	1·17	39·80%	447	0·96	32·65%	2·94
5	169	0·95	27·86%	374	1·33	39·00%	994	1·13	33·14%	3·41
6	139	0·735	26·39%	680	1·22	43·81%	718	0·83	29·80%	2·785
7	555	0·70	25·93%	575	1·08	40·0%	532	0·92	34·07%	2·7
T 8	628	0·95	36·8%	804	1·0	38·8%	457	0·63	24·4%	2·58
9	225	0·66	30·5%	264	0·80	36·8%	748	0·71	32·7%	2·17
10	113	—	—	147	—	—	885	—	—	—
11	435	1·21	38·1%	786	1·21	38·1%	605	0·76	23·9%	3·18
12	328	0·79	34·5%	184	0·74	32·3%	666	0·76	33·2%	2·29
13	690	1·06	38·4%	810	1·01*	36·6%	857	0·69	25·0%	2·76

T. = Day of steam-bath. * Afternoon fraction was lost; result was obtained by subtraction.



EXPERIMENT II. DIAGRAM 4. The upper series of figures show the amount of nitrogen in grm. per 8 hours excreted in the urine during the three periods of the day: 7 a.m.–3 p.m. (M.), 3 p.m.–11 p.m. (A.), 11 p.m.–7 a.m. (N.). The lower series of figures show the percentage amount of the total nitrogen which was excreted in each period.

from day to day. The percentage nitrogen output for the night period showed a considerable increase from 28·81 per cent. to 34·07 per cent. on the seventh day, and was also slightly irregular.

With a low nitrogen diet the period of the day during which the greatest amount of nitrogen is excreted seems to vary in different individuals, for, in

Experiment I on E. P. P., the greatest excretion always took place during the morning period. This peculiarity may perhaps be explained by the fact that the volume of the urine passed during the morning period in Experiment II was, with one exception, always much smaller than that passed in the other two periods of the day, whereas in Experiment I the volume of urine passed during the morning period was, with only one exception, much greater than that passed during the afternoon period.

Considerable changes took place in the diurnal variation on the temperature day. The bath was taken from 9.0 a.m. to 2 p.m., and the nitrogen excretion during the morning period was 0·25 grm., i.e. 10·97 per cent. higher than on the previous day. The nitrogen excretion during the afternoon period was slightly lower, while the excretion during the night period was 0·29 grm., i.e. 9·67 per cent. less than on the previous day. This change in the time of the nitrogen output was almost certainly caused by the change in the amount of urine secreted. Great frequency and precipitancy of micturition occurred during the bath, and a large amount of water was drunk. The volume of urine passed during the morning period was, with one exception, the largest recorded for the morning period of the day. The afternoon volume was also greater than usual; but much less urine than usual was passed during the night and two following eight-hourly periods.

Consequently the increase in the nitrogen output during the bath period was probably due to the urinary distress caused by the high temperature, and was compensated for by a diminished excretion during the night period.

On the day after the bath the diurnal variations in the nitrogen output had not returned to the usual type. The total nitrogen output was very low, 2·25 grm. (sum of fractions, 2·17 grm.). The percentage output for the morning period had fallen 6·3 per cent., but was still higher than usual; the output in the afternoon was lower than usual, while that of the afternoon period had risen 8·3 per cent. These changes are also probably due to the diminution in the volume of the urine excreted, which persisted during the morning and afternoon period, but was followed by a considerable diuresis during the night. Considerable variations occurred during the last three days, but they are probably accounted for by the disturbances in the diet which have already been referred to.

Experiment III. (Subject E. P. P.)

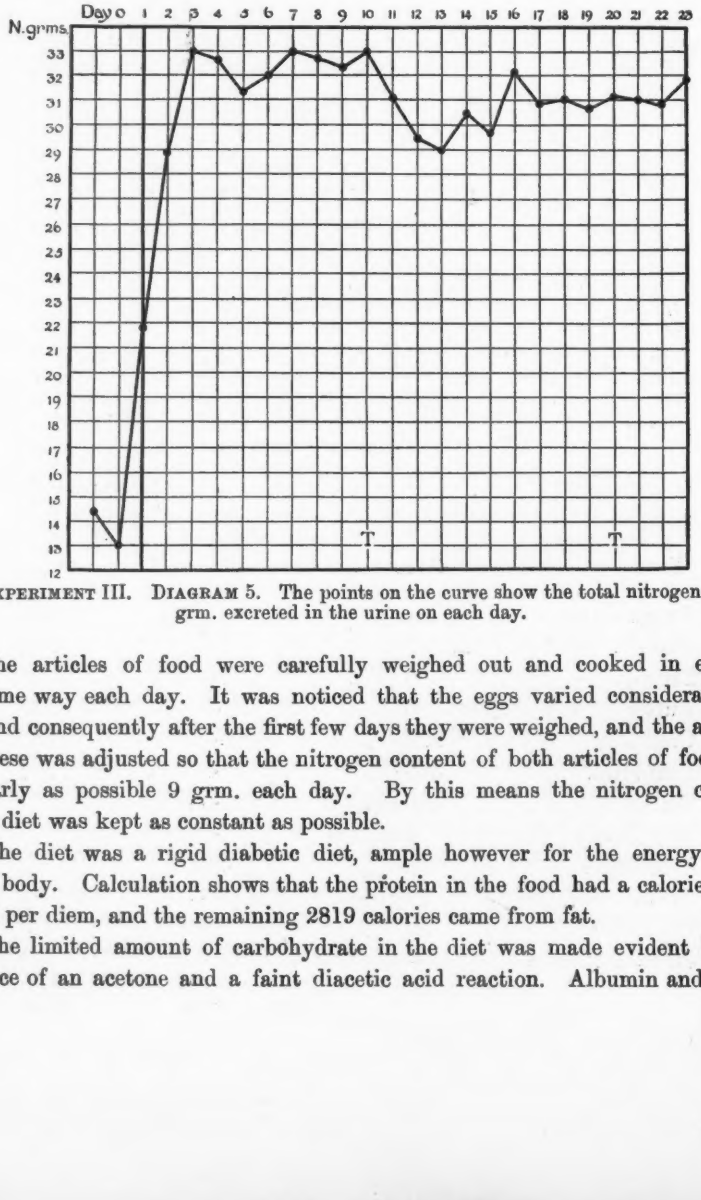
This experiment extended over a period of twenty-three days. The following diet was taken every day without exception:

Food.	Amount.	Nitrogen of food. Grm.	Calories.
5 eggs } when added together Cheese } nitrogen content } =		9·0	460 374
Plasmon	100 grm.	11·6	297
Butter	100 „	—	752
Cream	228 „	0·92	1000
Beaf-steak	365 „	11·68	724
Tea	400 c.c.	0·03	—
Maggi soup	4 tablets	0·55	—
Saccharine	2 „	0·01	—
Cocoa	18 grm.	0·65	94
Cucumber	50 „	—	—
Juice of 1 lemon	—	—	—
	Total	34·44	3701

Body weight at beginning of experiment . . = 73·4 kilos.
Body weight at end of experiment . . . . = 71·3 „
Calories per kilo at beginning of experiment . = 50·4
Calories per kilo at end of experiment . . . = 51·9

The meals were arranged as follows :—

Time.	Meal.	Nitrogen intake.
8.15 a.m.	Breakfast	8·75 grm.
12.45 p.m.	Lunch	13·78 „
4.30 p.m.	Two cups of tea and cream	0·03 „
7.30 p.m.	Dinner	8·81 „
9.45 p.m.	Supper	3·07 „



EXPERIMENT III. DIAGRAM 5. The points on the curve show the total nitrogen in grm. excreted in the urine on each day.

The articles of food were carefully weighed out and cooked in exactly the same way each day. It was noticed that the eggs varied considerably in size, and consequently after the first few days they were weighed, and the amount of cheese was adjusted so that the nitrogen content of both articles of food was as nearly as possible 9 grm. each day. By this means the nitrogen content of the diet was kept as constant as possible.

The diet was a rigid diabetic diet, ample however for the energy needs of the body. Calculation shows that the protein in the food had a calorie value of 882 per diem, and the remaining 2819 calories came from fat.

The limited amount of carbohydrate in the diet was made evident by the presence of an acetone and a faint diacetic acid reaction. Albumin and sugar

TABLE VII. *Experiment III. Subject E. P. P. Date, March 2–24, 1912.*

Day of Expt.	Weight in kilos.	N. of Food in grm.	Vol. of Urine in c.c.	Specific Gravity of Urine.	Total N. Grm.	Urea. Grm. of N.	Urea. % of total N.	Ammonia. Grm. of N.	Ammonia. % of total N.	Urea + Ammonia. Grm. of N.	Urea + Ammonia. % of total N.	Faeces. Grm. of N.	Nitrogen Balance. Grm. of N.	Acetone. Grm.	β-Oxybutyric acid. Grm.	β-Oxybutyric acid. % of total Acetone Bodies.	Total Acetone Bodies. Grm.
0		—	1690	—	14·39	—	—	—	—	—	—	—	—	—	—	—	—
0		—	1420	1020	12·92	—	—	0·60	4·64%	—	—	—	—	—	—	—	—
1	73·4	34·44	1539	1028	21·81	—	—	0·64	2·93%	—	—	—	+10·9 (approx.)	—	—	—	—
2		34·44	1727	1024	28·95	—	—	0·85	2·94%	—	—	1·74	+ 3·75	0·057	—	—	—
													+14·65 (Total)				
3		34·44	2054	1021	32·98	—	—	1·01	3·06%	—	—	1·74	− 0·28	—	—	—	—
4	72·8	34·44	2020	1025	32·77	—	—	1·04	3·17%	—	—	1·74	− 0·07	—	—	—	—
5		34·44	1922	1022	31·30	—	—	1·02	3·26%	—	—	1·74	+ 1·40	0·181	0·280	46·3%	0·605
6	72·4	34·44	1782	1027	32·02	—	—	1·02	3·19%	—	—	1·74	+ 0·68	0·104	0·153	45·1%	0·339
7		34·44	1905	1025	32·88	29·8	90·6%	1·04	3·16%	30·84	93·8%	1·82	Average − 0·26 = +0·21 per diem.	0·177	0·116	21·3%	0·433
8		34·53	2080	1022	32·77	29·21	89·1%	1·04	3·17%	30·25	92·3%	1·82	− 0·06	0·233	0·305	42·2%	0·723
9		34·60	2032	1023	32·31	29·0	89·8%	1·09	3·37%	30·09	93·1%	1·82	+ 0·47	0·222	0·320	44·6%	0·718
*10	71·3[1] / 73·2[2]	34·55	1869	1023	32·95	29·14	88·4%	1·18	3·58%	30·32	92·0%	1·82	− 0·22	0·325	0·571	49·5%	1·154
													+ 1·66 (Total)				
11	72·3	34·99	1820	1025	31·23	28·4	90·9%	1·08	3·46%	29·48	94·4%	1·68	+ 2·08	0·147	0·322	55·0%	0·586
12		34·47	1952	1022	29·47	—	—	1·08	3·67%	—	—	1·68	+ 3·32	0·249	0·262	37·0%	0·709
13		34·44	1860	1021	28·97	—	—	—	—	—	—	1·68	+ 3·79	0·180	0·363	52·9%	0·686
14	71·2	34·41	1995	—	30·46	—	—	—	—	—	—	1·68	Average + 2·27 = +2·58 per diem.	0·197	0·170	32·5%	0·523
15		34·57	1650	1025	29·77	—	—	—	—	—	—	1·68	+ 3·12	0·163	0·161	35·5%	0·453
16		34·81	2095	1022	32·22	—	—	—	—	—	—	1·68	+ 0·91	—	0·179	—	—
													+15·49 (Total)				
17	71·2	34·50	2057	1023	30·87	—	—	1·03	3·34%	—	—	1·68	+ 1·95	—	0·176	—	—
18		34·42	1880	1024	31·02	—	—	1·015	3·26%	—	—	1·68	+ 1·72	0·145	—	—	—
19		34·25	1990	1023	30·66	—	—	1·015	3·29%	—	—	1·68	+ 1·91	0·108	0·194	50·1%	0·387
*20	71·7[1] / 72·4[2]	34·27	1750	1024	31·17	—	—	1·064	3·40%	—	—	1·68	Average + 1·42 = 1·62 per diem.	0·322	0·363	38·6%	0·940
21	71·9	34·44	1664	1025	31·01	—	—	1·02	3·29%	—	—	1·77	+ 1·66	0·165	0·182	38·1%	0·478
22		34·44	1923	1022	30·82	—	—	1·00	3·24%	—	—	1·77	+ 1·85	0·0885	0·0704	30·6%	0·229
23	71·3	34·44	1990	1022	31·81	—	—	1·13	3·55%	—	—	1·77	+ 0·86	—	—	—	—
													+11·37 (Total)				

* Steam-bath taken on this day. Urea and ammonia of sweat (calculated) (1st 'temperature' day) = 0·356 grm. Urea and ammonia of sweat (2nd 'temperature' day) = 0·249 grm. [1] Before bath. [2] After bath.

were absent from the urine throughout the experiment. The urine was always acid to litmus. The subject of the experiment felt perfectly fit throughout, though his breath soon became unpleasant, and his tongue became furred. For the first day or two carbohydrates were missed, but later the diet became more palatable, though at best it was not eaten with great relish.

Table VII shows the nitrogen balance throughout the whole period of the experiment. The curve in Diagram 5 shows the daily nitrogen in the urine.

The body attained nitrogen equilibrium on the third day of the diet. During the first two days a retention of about 14·65 grm. of nitrogen took place; and this retention always occurs on passing from a lower level to a higher level of nitrogen equilibrium (Gruber (10)).

The nitrogen equilibrium was maintained until the tenth day, i.e. the day of the first steam-bath. The nitrogen excretion during this period was not very constant, but the extreme limits of the variations fall within 1·7 grm., i.e. 5 per cent. of the amount excreted. When it is considered, however, that the organism was suddenly called upon to deal with nearly three times the amount of protein that it was accustomed to, these variations are comparatively small.

On the eleventh day a period of much greater irregularity supervened and lasted six days. The limit of variation in the nitrogen output was 3·25 grm., i. e. nearly 10 per cent. There was a daily retention of nitrogen, the total amount retained during the period being 15·49 grm., i. e. 2·58 grm. per day.

On the seventeenth day a period of constant nitrogen excretion began, and was accompanied by a further nitrogen retention of 11·37 grm. in seven days, i.e. 1·62 grm. per day. During this period the second bath was taken.

Lüthje (20) has recorded a similar case.

A man, who had three months earlier recovered from an attack of typhoid fever and had since been quite healthy, was given a constant diet containing 30·78 grm. of nitrogen. For the first eight days there was a + balance of 0·32 grm., showing that the body was in nitrogen equilibrium. For the next six days there was a nitrogen retention of 2·47 grm. per day.

In another experiment a woman was fed with a diet containing 49·95 grm. of nitrogen. There was no preliminary period of nitrogen equilibrium, as the body retained nitrogen, at the rate of 16·0 grm. per diem, from the very beginning.

Bornstein (3) and other authors have succeeded in obtaining a nitrogen retention, when comparatively small amounts of nitrogen were taken in the food (20 grm. or less); and this retention is regarded by them as meaning that new protoplasm has been built up in the body. If the nitrogen retention in Experiment III and in Lüthje's case is regarded as due to a definite formation of protoplasm, the preliminary period of nitrogen equilibrium can only be accounted for by considering that the body could not at once, for some reason, avail itself of this opportunity of forming new protoplasm. For eight days it excreted the whole of the nitrogen of the food; and it was only after this period that the synthesis of body protoplasm began.

A more probable explanation of these two cases lies in the fact that suddenly giving a diet of over 30 grm. of nitrogen increased the work to be performed by the kidneys. They acted satisfactorily to begin with, so that nitrogen equilibrium was maintained for several days; but subsequently their excretory powers failed to some extent, and a steady nitrogen retention occurred.

In Lüthje's second experiment, the patient was given a diet containing a still larger amount of nitrogen (49·95 grm.), and nitrogen retention began at once. If the second and more probable explanation is accepted, it would mean that in this case so much nitrogen was given that the body was unable to excrete it all, even to begin with.

There is no doubt, from the investigations of Hale White and Spriggs (13) on a woman, that when much larger amounts of nitrogen are given than were employed in Experiment III, a retention of all the nitrogen in the form of protoplasm is impossible, because the weight of body tissue formed would be greater than the increase of body weight actually found. A similar result has been obtained in man by Lüthje and Berger (21) and A. Müller (30); but there is no definite evidence as to whether, under these conditions, nitrogen is retained in the form of protein or of simpler nitrogen compounds.

It may have been a pure coincidence that the period of nitrogen retention, in the case of E. P. P., started on the day after the first bath, because the second 'temperature' day produced no such change, and in Lüthje's case the period of nitrogen retention began when no bath had been taken. On the other hand, it is possible that the bath may have had a disturbing effect on the metabolism, and the oedema noticed immediately after the bath is perhaps in favour of this view.

The first bath was taken on the tenth day. The rectal temperature reached 102·2° F. (39° C.) in a little over 1½ hours after entering the bath. During this period the wet-bulb thermometer remained between 96·8° F. and 98·6° F. (36° C. and 37° C.). After a short time the amount of steam was very much diminished, but the rectal temperature continued to rise, and after reaching 103·3° F. (39·6° C.) it gradually fell to 102·2° F. (39° C.). At this point the steam was turned on again, and the rectal temperature again rose to 103° F. (39·47° C.), after having fallen to 101·8° F. (38·8° C.). The highest temperature obtained was 103·4° F. (39·65° C.), while the temperature remained above 102·2° F. (39° C.) for nearly 3¾ hours. The pulse remained high throughout, but the respirations were low.

The second bath was taken on the twentieth day. The rectal temperature rose slowly at first, as the wet-bulb reading remained for some time between 95° F. and 96·8° F. (35° C. and 36° C.). The steam was then increased, and the temperature rose more quickly. A considerable amount of distress was felt. The highest temperature obtained was 104·2° F. (40·13° C.), while the rectal temperature was above 102·2° F. (39° C.) for over 2 hours, and over 103·1° F. (39·5° C.) for 1 hour.

The total nitrogen excretion of the three days previous to the first bath was fairly constant, and, including the nitrogen of the faeces, the average was 34·47 grm. The nitrogen in the urine on the first 'temperature' day was 32·95 grm., and, together with the faecal nitrogen and the calculated value for the urea and ammonia of the sweat, the total nitrogen output was 35·13 grm., i. e. 0·66 grm. higher than the average of the three preceding days.

The second bath was taken on the twentieth day. The average of the total nitrogen output, including the faecal nitrogen, for the three previous days and the two succeeding days was 32·59 grm. On the second 'temperature' day the output in the urine was 31·17 grm., and, with the urea and ammonia nitrogen of the sweat and the faecal nitrogen, the value was 33·10 grm., and this is

0·51 grm. above the average for the other days. From these figures it is reasonable to conclude that a slight rise in the nitrogen output took place on both occasions in this experiment as the result of the baths.

The absence of carbohydrates from the diet caused an excretion of acetone, aceto-acetic acid, and laevo-rotatory β-oxybutyric acid in the urine, and these substances were estimated throughout most of the experiment, and the results are shown in Table VII. In the column headed 'Total acetone bodies' the excretions of β-oxybutyric acid and acetone are reckoned together, the latter being calculated as β-oxybutyric acid.

The amount of acetone in the urine was 0·181 grm. on the fifth day of the experiment, and remained less than 0·2 grm. for the next two days. On the eighth and ninth days the amount rose above 0·2 grm., and on the tenth day (first 'temperature' day) a further rise to 0·325 grm. took place, the amount excreted being 0·1 grm. more than the average of the two preceding days. On the eleventh day the excretion fell to 0·147 grm., and rose again on the following day to 0·249 grm., and then gradually fell until, on the nineteenth day, it was only 0·108 grm. On the twentieth day (second 'temperature' day) a rise of 0·2 grm. occurred, 0·322 grm. being excreted altogether. On the next day the excretion fell to 0·165 grm., and on the day after to 0·0885 grm.

The behaviour of the β-oxybutyric acid was very similar. From the fifth to the seventh days the amount excreted was less than 0·3 grm.; on the next two days the excretion was over 0·3 grm., and on the 'temperature' day a rise of 0·26 grm. above the average of the two preceding days took place, the amount of β-oxybutyric acid excreted being 0·571 grm. on this day. It will be seen that the total acetone bodies rose on this day from 0·72 grm. to 1·15 grm., i. e. a rise of 0·43 grm. occurred.

On the day after the first bath the excretion of β-oxybutyric acid fell to 0·322 grm., and it remained about the same level for two more days. The excretion then fell below 0·2 grm., and remained at about this amount until the second 'temperature' day, when a rise of 0·169 grm. occurred, the amount excreted being 0·363 grm. on this day. The total acetone bodies showed a rise of 0·55 grm. on this day, i. e. the excretion rose from 0·387 grm. to 0·940 grm., and this rise is larger than that which occurred on the first 'temperature' day.

On the day after the second bath the amount of β-oxybutyric acid in the urine fell to 0·182 grm., and on the next day a further fall to 0·0704 grm. took place.

The significance of the alteration in the acidosis, as shown by the behaviour of the acetone and the β-oxybutyric acid excretions, will be discussed later with the results of Experiment IV.

The amount of β-oxybutyric acid excreted has also been calculated as a percentage of the total acetone bodies for each day. These percentages show considerable variations, usually lying between 20 per cent. and 50 per cent., and no special rises in the percentages were observed on the 'temperature' days in this experiment.

The amount of the nitrogen excreted in the form of ammonia was determined throughout most of the experiment. On the day before the experiment began 0·60 grm. of ammonia nitrogen was excreted on the ordinary mixed diet. The ammonia gradually rose from the beginning of the experiment, and on the third day it had reached 1·01 grm. nitrogen. This rise of 0·4 grm. indicated an additional formation of acid substances in the body. The amount of β-oxybutyric acid excreted on the third day was 0·280 grm., but calculation shows that only 0·038 grm. of ammonia nitrogen was required to neutralize this amount of acid. Hence by far the greater part of this acidosis was not due to the formation of acetone bodies, but to other acid substances produced by the special diet of the experiment.

From the fourth to the eighth days the amount of ammonia varied between 1·02 grm. nitrogen and 1·04 grm. nitrogen. On the eighth day a rise was observed in the excretion of the total acetone bodies, and a corresponding rise in the ammonia to 1·09 grm. nitrogen took place on the ninth day. On the first 'temperature' day the ammonia rose to 1·18 grm. nitrogen, and fell on the next day to 1·08 grm. nitrogen, which shows that the increase in the acidosis due to the bath was followed by a return to the same level as that immediately preceding the bath. No ammonia estimations were carried out for the next four days, and on the seventeenth to nineteenth days the ammonia varied from 1·015 to 1·03 grm. nitrogen, which showed that it had fallen to the same level as at the beginning of the diet.

The rise in the excretion of ammonia and total acetone bodies before the first bath indicated a progressive increase in the acidosis of the body, which was due presumably to the diet. The gradual fall in the acidosis after the bath indicated that the body adapted itself to the diet, probably by modifying its fat metabolism in some way.

On the second 'temperature' day the ammonia showed a rise of 0·05 grm. nitrogen, and 1·064 grm. nitrogen were actually excreted. This increase was not so great as that on the first 'temperature' day, although the excretion of acetone bodies showed a larger rise on the second 'temperature' day. On the two days following the second bath the ammonia excretion fell to 1·02 grm. nitrogen and 1 grm. nitrogen respectively. There is no explanation of the marked rise in the ammonia nitrogen excretion on the last day of the experiment. It will be noticed that the total nitrogen excretion, which had been constant for several days previously, also rose on this day.

The urea excretion was estimated from the seventh to the eleventh days of the experiment. The amount varied between 28 and 30 grm. nitrogen. Its percentage of the total nitrogen was 90·6 per cent. on the seventh day, 89·1 per cent. on the eighth day, and 89·8 per cent. on the ninth day. On the first 'temperature' day a fall to 88·4 per cent. was observed, and on the next day the percentage rose again to 90·9 per cent. The amounts of nitrogen excreted as urea and ammonia have also been calculated as a percentage of the total nitrogen in Table VII. On the eighth, ninth, and 'temperature' days, these percentages

were fairly constant, 92·3 per cent. to 93·1 per cent., showing that the increase in the ammonia excretion, as a result of the bath, was more or less compensated for by a diminution in the urea excretion.

The amount of nitrogen excreted during the three eight-hourly periods are shown in Table VIII and by the upper series of figures in Diagram 6.

The periods extended from 7.30 a.m. to 3.30 p.m., from 3.30 p.m. to 11.30 p.m., and from 11.30 p.m. to 7.30 a.m.

The lower series of figures show what percentage of the total nitrogen was excreted during each period.

The fractions are divided into two series, corresponding to the two 'temperature' days in this experiment.

TABLE VIII. *Experiment III. Fractions.*

Day of Expt.	Morning Period. 7.30 a.m.–3.30 p.m.			Afternoon Period. 3.30 p.m.–11.30 p.m.			Night Period. 11.30 p.m.–7.30 a.m.			Total N., i.e. sum of fractions.
	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	Vol. of Urine. c.c.	N. of Urine. grm.	% of total N.	
3	786	10·69	32·4 %	836	13·07	39·6 %	432	9·34	28·3 %	33·0
4	—	—	—	—	—	—	—	—	—	—
5	607	9·85	31·5 %	810	12·66	40·6 %	505	8·71	27·9 %	31·22
6	630	10·44	32·7 %	740	12·13	38·0 %	412	9·34	29·3 %	31·91
7	—	—	—	—	—	—	—	—	—	—
8	—	—	—	—	—	—	—	—	—	—
9	805	10·80	33·6 %	787	12·38	38·5 %	440	8·97	27·9 %	32·15
10*	612	9·76	29·9 %	885	14·16	43·4 %	372	8·69	26·7 %	32·61
11	574	9·58	31·0 %	720	12·23	39·6 %	526	9·11	29·5 %	30·92
12	720	9·32	31·9 %	782	11·34	38·8 %	450	8·60	29·4 %	29·26
18	700	10·12	32·8 %	725	11·75	38·1 %	455	9·00	29·1 %	30·87
19	765	10·35	33·4 %	795	11·93	38·5 %	430	8·71	28·1 %	30·99
20*	592	9·66	31·0 %	778	13·12	42·1 %	380	8·36	26·9 %	31·14
21	554	10·09	32·7 %	695	11·93	38·6 %	415	8·85	28·7 %	30·87
22	610	9·60	31·2 %	785	12·55	40·8 %	528	8·58	27·9 %	30·73
23	660	9·85	31·2 %	815	13·39	42·5 %	515	8·25	26·3 %	31·49

* Bath taken on this day.

The fractions for the fourth, seventh, and eighth days are not given, as on these days, owing to an error, the bladder was not emptied punctually at 3.30 p.m. or 11.30 p.m.; and the results are untrustworthy for purposes of comparison.

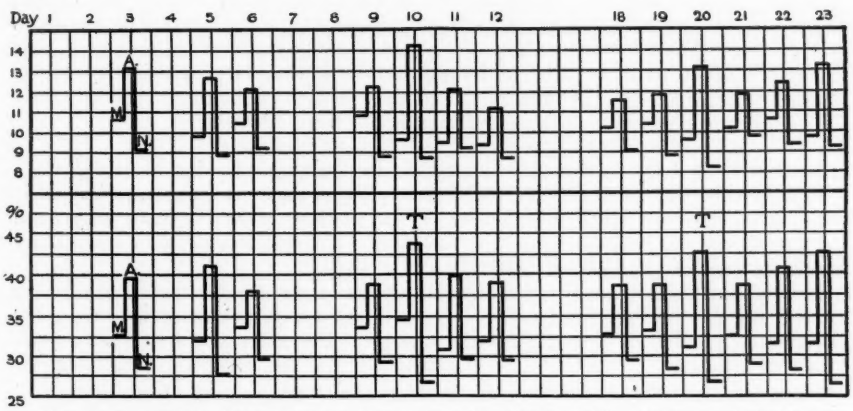
In the case of all the fractions, the greatest amount of nitrogen was excreted during the afternoon period. From the Table of Meals at the beginning of the experiment it will be seen that the heaviest meal was taken at 12.45 p.m., when food containing 13·78 grm. of nitrogen was eaten. Gruber (10) has shown that in a dog the maximum elimination of nitrogen after a meal of meat takes place between five and seven hours after feeding. Wolf (41) found that in man the nitrogen elimination from a meal of veal cutlets began one hour after the meal and reached a maximum eight hours after the meal had been eaten.

These observations indicate that the period of maximum nitrogen excretion due to the heaviest meal of the day would take place between 7 p.m. and 9 p.m., i.e. about the middle of the afternoon period, and this is sufficient to explain the

fact that the largest amount of nitrogen was always excreted during this period of the day.

In the first series of fractions, with the exception of the first 'temperature' day, the amounts of nitrogen excreted for corresponding periods, when calculated as percentages of the total nitrogen, were fairly constant, but showed slight variations. The greatest variations were observed on the first 'temperature' day, though the meals were taken at the usual times. As the fractions for the seventh and eighth days are missing, it seems best to compare the fractions of the first 'temperature' day with those of the day before in order to realize the size of the variations.

The amount of nitrogen excreted during the morning was 9·76 grm., i. e. 1·04 grm. less than that during the same period of the day before, and the percentage amount excreted was 3·7 per cent. less. In the afternoon the amount excreted was 1·78 grm. greater, and the percentage amount was 4·9 per cent. greater than that for the afternoon period of the day before. The nitrogen excreted for the night period on the 'temperature' day showed a slight diminution



EXPERIMENT III. DIAGRAM 6. The upper series of figures shows the amount of nitrogen in grm. per 8 hours excreted in the urine during the three periods of the day: 7.30 a.m.–3.30 p.m., 3.30 p.m.–11.30 p.m., 11.30 p.m.–7.30 a.m. The lower series of figures represents the percentage amounts of the total nitrogen which were excreted during each period of the day. Note: The results for the fourth, seventh, and eighth days are untrustworthy, and are not included.

of 0·28 grm., and the percentage also fell slightly. It has been pointed out that the total amount of nitrogen excreted on the 'temperature' day was 0·66 grm. above the average of the preceding three days. On the 'temperature' day a great rise took place during the afternoon period, when 1·78 grm. more nitrogen were excreted than on the day before. It is quite likely that part of this rise may be accounted for by this small increase in the total nitrogen excretion obtained on this day. On the other hand, the diminution during the morning period shows that the greater part of this rise was probably due to the fact that the bath produced some delay in the nitrogen metabolism of the food. Lunch was taken at the usual time, i. e. 12.45 p.m., during the bath, which was not over till 3 p.m. If in this case the food metabolism had been delayed to some extent, the excretion of nitrogen from 3.30 p.m. to 11.30 p.m. would be larger than usual, and at the same time the excretion in the morning period would be diminished.

A consideration of the fraction curves in the last half of the experiment supports the hypothesis that delayed metabolism was responsible for the greater part of the increase during the afternoon of the first 'temperature' day.

On the eighteenth, nineteenth, and twenty-first days the customary time-table for meals was strictly adhered to, and the percentage amounts of nitrogen excreted were very constant. On the second 'temperature' day an attempt was made to take lunch at 12.45 p.m., but owing to some distress and a feeling of nausea only about half the food could be eaten, and the remainder was finished after the bath between 2.15 p.m. and 2.30 p.m. The excretion in the afternoon was markedly increased, while in the morning it was diminished, a result similar to that of the first 'temperature' day. The night output was also less than usual, but this is probably explained by the fact that dinner was taken 1¼ hours earlier than usual.

In order to test this hypothesis further, the meals on the twenty-second and twenty-third days of the experiment were taken in exactly the same manner as on the second 'temperature' day. The percentage amounts of nitrogen excreted for all these three days are very similar indeed to one another.

Hence an increase in the afternoon's output, at the expense of the morning's output, was obtained on the first 'temperature' day, when lunch was taken at the usual time during the bath, and on the second 'temperature' day, when lunch was only partly eaten at the usual time and finished later. The curve in this latter case was exactly simulated by taking meals at the same times on two days when ordinary routine laboratory work was being performed. This shows that the result of an artificial rise of temperature is to cause a definite delay in the nitrogen metabolism of the food.

There are two possible causes of this delay in metabolism:

(1) A delay in the process of digestion or assimilation.

(2) A delay in the excretion of the food nitrogen by the kidneys.

It is difficult to decide which of these two hypotheses is correct, although it is possible that the slight oedema which was noticed after the bath may have indicated that the kidneys were not excreting quite satisfactorily; on the other hand, no trace of albumin was detected in the urine.

It is true that, in this experiment, there was some frequency of micturition during the baths; but the volume of urine passed, unlike that in the other experiments, remained about the same as usual. The afternoon's volume on the first 'temperature' day was slightly increased, and the night's volume slightly diminished, but it is unlikely that these slight changes can have materially altered the amount of nitrogen excreted.

The main difference between this and the two earlier experiments was that in this experiment by far the greatest amount of nitrogen excreted was derived directly from the nitrogen of the food, and there was a definite delay in this metabolism. In Experiments I and II the nitrogen of the food can have taken but a small part in the nitrogen metabolism, and the variations in the nitrogen excretion observed can be explained entirely by alterations in the volume of urine excreted.

Experiment IV. (Subject G. G.)

The constant daily diet employed in this experiment was deficient in calorie value and contained very little carbohydrate.

Plasmon	80 grm.	9·18 grm. N.	296 cal.
Cocoa	17 „	0·7 „ „	88 „
Cream	342 „	1·39 „ „	1500 „
Egg	1	1·0 „ „	85 „
Salt	12 grm.	0 „ „	0 „
		12·27 grm. N.	1969 cal.

Calories per kilo—

At the beginning of the experiment . . . . = 31·8 cal.
At the end of the experiment . . . . . = 33·3 „

The plasmon, cocoa and salt were thoroughly mixed together, and then divided into three equal parts. When mixed with boiling water and cream the diet was quite palatable. The egg was eaten at the midday meal either boiled or beaten up with cream. The meals were regularly eaten at 7.30 a.m., 1 p.m. and 7 p.m. The quantity of fluid taken was not measured, but approximately the same number of cups of cocoa were drunk each day. This diet caused considerable discomfort, and the hunger pains after each meal for the first two days were very severe. After the third day the food seemed more satisfying, and gave no more trouble until the tenth and eleventh days, when some gastric discomfort was felt causing very uneasy sleep. During the first five days an increasing sensation of weakness, especially in the knees, was felt, and it was an effort to do anything in a hurry, but no difficulty was found in working in the laboratory from 8.30 a.m. until 4 p.m. After the sixth day the feeling of weakness seemed to get less each day, but a sensation of 'chilliness' was noticed. For several days after the experiment no appetite was felt for the ordinary mixed diet, and the sensation of weakness did not pass off altogether for more than ten days. No sugar or albumin were excreted in the urine at any time.

The body weight fell one kilo during the first day, but afterwards more slowly, as only 3·6 kilos were lost during the eleven days. The weight increased 0·3 kilo during the fever period, but on this occasion no puffiness of the face was observed.

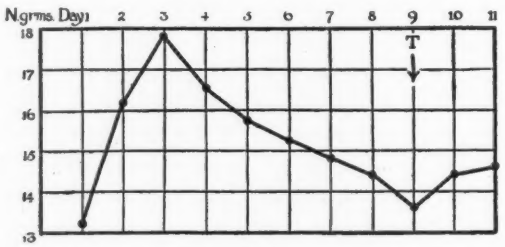
The temperature was produced on the ninth day. A rectal temperature of 102·2° F. (39° C.) was reached after 3¼ hours and 103·4° F. (39·65° C.) after 3¾ hours. A temperature over 102·2° F. (39° C.) was maintained for 2½ hours and over 103° F. (39·45° C.) for 2 hours. The temperature would not rise above 103·4° F. (39·65° C.) although the room temperature (wet-bulb thermometer) remained continuously at or slightly over 36° C. for nearly 4 hours, and at one time reached 38° C. for about 20 minutes, and a short time afterwards reached 40° C. for about 20 minutes. The difficulty found in raising the body temperature was probably due to the depression of the general metabolism of the body as a result of the semi-starvation. This was also shown by the feeling of chilliness which was present after the sixth day, and was especially marked on the evening and night of the temperature day. A little more difficulty was felt in bearing the conditions of the bath than in Experiment II on the same individual, but a little less weakness was experienced afterwards.

The total nitrogen excreted in the urine on the ordinary diet before the experiment began was 11·04 grm., and the semi-starvation diet caused a greatly increased output. The curve of the nitrogen output (Table IX, Diagram VII) rose steeply for the first three days to 17·84 grm., and then fell for the

TABLE IX. *Experiment IV.*

Day of Expt. Weight in kilos.	Vol. in c.c.	Total N. Grm.	Urea. Grm. of N.	Urea. % of total N.	Ammonia. Grm. of N.	Ammonia. % of total N.	Urea + Ammonia. Grm. of N.	Urea + Ammonia. % of total N.	Uric Acid. Grm.	Uric Acid. Grm. of N.	Uric Acid. % of total N.
0	1420	11·04	—	—	—	—	—	—	—	—	—
1 } 62·4 }	2098	13·25	12·03	90·79%	—	—	—	—	—	—	—
2 } 61·3 }	960	16·19	14·26	88·08%	0·34	2·1%	14·6	90·18%	0·282	0·094	0·58%
3	1213	17·84	15·97	89·52%	0·39	2·19%	16·36	91·71%	0·315	0·105	0·59%
4 } 60·6 }	1250	16·58	15·07	90·89%	0·28	1·69%	15 35	92·58%	0·408	0·136	0·82%
5	1521	15·77	14·3	90·68%	0·39	2·47%	14·69	93·15%	0·252	0·084	0·53%
6 } 60·4 }	1796	15·26	13·58	89·01%	0·43	2·82%	14·01	91·83%	0·255	0·085	0·56%
7	1774	14·87	13·63	91·66%	0·39	2·62%	14·02	94·28%	0·231	0·077	0·52%
8	1663	14·31	12·70	88·75%	0·43	3·0%	13·13	91·75%	0·207	0·069	0·48%
T 9 } 59·2 } 59·5 }	1213	13·62*	11·9	87·37%	0·62	4·55%	12·52	91·92%	0·171	0·057	0·42%
10	1537	14·39	12·52	87·0%	0·59	4·1%	13·11	91·1%	0·399	0·133	0·92%
11 } 58·8 }	2285	14·51	—	—	0·461	3·18%	—	—	0·507	0·169	1·16%

T Steam-bath taken on this day. * Urea and ammonia of sweat = 13·89 grm.



EXPERIMENT IV. DIAGRAM 7. The points on the curve show the total nitrogen in grm. excreted in the urine on each day.

next five days, reaching 14·31 grm. on the eighth day. A further fall to 13·62 (or with the addition of the urea and ammonia nitrogen of the sweat 13·89 grm.) occurred on the temperature day, but was followed by a rise to 14·39 grm. on the next day and to 14·51 grm. on the second day after the bath.

Hence there was no rise in the nitrogen excretion as a result of the bath on the temperature day itself. The average negative balance for the last four days of the experiment was 31·7 grm. It is reasonable to suppose that this daily loss represents the nearest approach towards nitrogen equilibrium that the body could make, in view of the low calorie value of the diet. The actual fall in the nitrogen excretion on the temperature day probably lies within the limits of the

Date, March 23–*April* 4, 1912.

Creatinine.			Undetermined N.		Faeces.	Nitrogen Balance.	Acetone.	β-oxybutyric Acid.		Total Acetone Bodies. Reckoned as β-oxybutyric Acid. Grm.	Day of Expt.
Grm.	Grm. of N.	% of total N.	Grm. of N.	% of total N.	Grm. of N.	Grm. of N.	Grm.	Grm.	% of total Acetone Bodies.		
—	—	—	—	—	—	—	—	—	—	—	0
—	—	—	—	—	1·37	−2·35	—	—	—	—	1
1·51	0·56	3·46%	0·936	5·58%	1·37	−5·29	0·278	0·199	22·6%	0·699	2
1·35	0·50	2·8%	0·875	4·9%	1·37	−6·94	0·296	0·311	36·8%	0·844	3
1·614	0·60	3·62%	0·494	2·98%	1·37	−5·68	0·305	0·328	37·4%	0·877	4
1·59	0·59	3·74%	0·406	2·58%	1·37	−4·87	0·442	0·593	43·7%	1·389	5
1·43	0·53	3·47%	0·635	4·16%	1·37	−4·36	0·389	0·329	32·7%	1·029	6
1·43	0·53	3·56%	0·243	1·63%	1·37	−3·97	0·382	0·454	39·8%	1·142	7
1·51	0·56	3·82%	0·551	3·85%	1·37	−3·41	0·418	0·466	39·5%	1·208	8
1·43	0·53	3·89%	0·513	3·76%	1·1	−2·45	0·838	2·66	63·7%	4·17	9 T
1·46	0·52	3·61%	0·627	4·36%	1·1	−3·22	0·249	0·656	59·4%	1·104	10
—	—	—	—	—	1·1	−3·34	0·366	0·251	27·6%	0·91	11

T Steam-bath taken on this day.

daily variations. It may be argued that, although no additional nitrogen was excreted on the temperature day, some protein was broken down, and the nitrogen was excreted on the next (tenth) day. This, it is true, would account for the small rise which occurred on the tenth day, but in this case the nitrogen output on the eleventh day should have been down to the level of the 'temperature day', whereas it was 0·62 grm. higher than on that day, and 0·12 grm. higher than on the tenth day. Moreover, in Experiment III, the slight rise, which probably took place, occurred on the temperature day itself.

As in Experiment III, β-oxybutyric acid, diacetic acid and acetone were excreted in the urine. The acetone was not estimated on the first day, but amounted to 0·278 grm. on the second day. It increased gradually to 0·442 on the fifth day, and in the next three days only varied between 0·389 and 0·418 grm. The β-oxybutyric acid was very small in amount on the second day, but reached 0·311 grm. on the third day, and formed 36·8 per cent. of the total acetone bodies, reckoned as β-oxybutyric acid. During the next five days it oscillated between 0·328 grm. and 0·593 grm., forming between 32·7 per cent. and 43·7 per cent. of the total output of acetone bodies. The total output of acetone bodies reached 1·389 grm. on the fifth day and remained above 1·0 grm. during the next three days. On the temperature day the total output of the acetone bodies rose from 1·208 grm. to 4·17 grm.; the acetone output from 0·418 to 0·838 grm.; the β-oxybutyric acid from 0·466 grm. to 2·66 grm., and formed 63·7 per cent. of the total output. On the next day the total output fell to 1·104 grm.; the β-oxybutyric acid to 0·656

grm., and still formed 59·4 per cent. of the total output. This experiment confirms the observation of O. Neubauer that, if the total output of acetone bodies is high, the percentage share of the β-oxybutyric acid is between 60 and 80 per cent., but when the total output is low the percentage share is less.

The marked increase in the total output of acetone bodies on the temperature day in this experiment and the smaller but definite increase in Experiment III were undoubtedly due to the high temperature. The acetone bodies must have been produced by the increased utilisation of either protein, carbohydrate, or fat. The increased output cannot be derived from the protein metabolism, as no increase in the latter took place. Moreover, Magnus Levy (22) has proved in cases of diabetes that the β-oxybutyric acid cannot all come from the proteins, but must be largely derived from the fat. The work of L. Schwarz (35), O. Neubauer (26), and L. Blum on the amino acids has greatly aided the hypothesis that the β-oxybutyric acid is formed as an intermediate stage of fat-burning. In healthy people this burning is completely performed. However, under conditions either of lack of carbohydrate or of carbohydrate which is not accessible, e.g. diabetes and phloridizin diabetes, the fat is not completely burnt, but appears as β-oxybutyric acid together with further stages of decomposition, aceto-acetic acid and acetone.

An increased β-oxybutyric acid output may be produced in two ways:

1. An increase in the consumption of fat.
2. A decrease in the store of carbohydrates available in the body.

An artificially produced high temperature has been shown by Sutton (38) to cause a great increase in the respiratory exchange and a rise in the respiratory quotient. This means that the high temperature caused a great increase in the energy production, and that the carbohydrate took the chief share in the increased energy production, but some additional fat was also consumed. It is not possible from Sutton's results to say how much carbohydrate and fat were actually burnt, as no nitrogen determinations were made. All Sutton's experiments were carried out on an ordinary mixed diet, and the high temperature was produced after a period of fasting, which lasted seventeen to twenty hours. While this period is long enough to get rid of the effects of the last meal on the respiratory exchange, it is not long enough to reduce materially the amount of available carbohydrate in the body. In our experiment, however, the body had been in a state of semi-starvation for eight days before the high temperature was produced, and the carbohydrate store of the body must have been considerably depleted. Consequently more fat must have been burnt throughout the experiment. It is therefore reasonable to suppose that, on the temperature day, a considerable increase in the fat-burning took place, and consequently more β-oxybutyric acid was excreted.

On the other hand, it is conceivable that a great decrease in the already much depleted store of carbohydrate occurred on the temperature day, and in consequence a much larger percentage of fat was incompletely burnt and

excreted as β-oxybutyric acid, although no increase in the fat consumption took place. As no respiratory experiments were made in the experiment, it is impossible to say which of these two hypotheses is correct, but for the reasons already given it seems much more probable that the rise of the β-oxybutyric acid output was due to an actual increase in the fat consumption.

The complete nitrogen distribution was determined in this experiment, and showed considerable changes on the temperature day. The percentage of the urea and ammonia nitrogen added together was fairly constant throughout the experiment, and on the eighth to tenth days only varied from 91·1 per cent. to 91·9 per cent. of the total nitrogen. The ammonia output oscillated a little during the first eight days, varying from 0·28 to 0·43 grm. nitrogen, but on the temperature day it rose to 0·62 grm. nitrogen, and only fell slightly on the next day, and was still a little raised on the second day after the bath. The fall in urea nitrogen output which occurred on the temperature and succeeding day was almost exactly balanced by the increase in the ammonia nitrogen, and agrees with the changes observed in Experiment II. The rise in the ammonia output is undoubtedly due to an increase in the acidosis. Some acidosis existed throughout the experiment, since β-oxybutyric acid was excreted, and the increased output of ammonia on the temperature day can be explained by the increase in the β-oxybutyric output on this day. But the persistence of the ammonia output at the same level on the next day cannot be accounted for in this way, as the β-oxybutyric acid had fallen to a small amount. A possible explanation is that the high temperature produced some other acid body, and that this was either still being formed during the next day or was still being gradually excreted. In support of this hypothesis is the rise in the ammonia output in Experiment II, the fall of the percentage amount of the urea nitrogen in Experiment I, which cannot be explained by the presence of the acetone bodies, as no acetone was detected.

The diet in this experiment was not purin free, as 17 grm. of cocoa containing some theobromine were taken each day. The theobromine cannot have had any influence, however, as the uric acid output was slightly less in this experiment than in Experiment II on the same individual, when a purin-free diet was being eaten.

The uric acid output fell steadily, with the exception of a rise on the fourth day, and on the eighth day 0·207 grm. was excreted, i. e. practically the same amount as in Experiment II on the same individual. The output fell on the temperature day to 0·171 grm., but was followed by a rise to 0·396 grm. on the first day after the bath, and a further rise to 0·507 grm. on the second day. This result occurring on the day after the fever was unexpected, and, owing to the time taken in the estimation (two days), the diet had been given up before the significance of the result was realized. A rise in the uric acid output takes place during fevers, and the experiments of Leathes (18) with the pyrexia produced by a typhoid inoculation show that the increase takes place within a few hours of the rise of temperature. Linser (19), who was not eating

a purin-free diet, obtained a small rise of 0·06 grm. in Experiment I, which was most obvious on the third day of the three successive temperature days, but was followed by a sudden fall on the next day. In his last experiment he obtained a rise of 0·06 grm. on the day after the temperature.

This increased output cannot be attributed directly to the effect of the high temperature itself, as the results of Experiments I and II have shown that high temperature by itself does not cause an increased uric acid output. The fact that in Experiment IV the increase occurred on the first day after the temperature, and was still higher on the second day, makes this hypothesis very unlikely. The cause of the increased uric acid output is not very obvious, but it may have been due to other changes in the metabolism as a result of the high temperature, and therefore be an indirect sequel of the high temperature.

It has already been shown that the β-oxybutyric acid output was greatly increased on the temperature day, but that it fell on the next day to the usual amount. The ammonia output, however, was increased on the temperature day, and was almost as high on the next day, showing that the acidosis still existed. It is possible that the acidosis, which thus existed for two days, may have caused the rise in the uric acid output. In support of this hypothesis are the changes described in diabetes. In mild cases no alterations in the uric acid output take place, but in the severe cases, i. e. where acidosis occurs, the uric acid output is much increased. Von Noorden (28) considered that this increase was due to toxic causes. He also pointed out that in some cases the uric acid output was sometimes increased, while the body was actually retaining nitrogen. He therefore concluded that the toxic process, which affected the uric acid metabolism, did not influence the total nitrogen output.

Cathcart (5) has estimated the uric acid output in a starving man. The output fell to 0·18 grm. on the second and third day; on the fourth day it rose to 0·24 grm., and then steadily increased to 0·51 grm. on the twelfth day. In this case, as in all starving people, acetone and diacetic acid were present, and a considerable degree of acidosis must have existed, because the ammonia output, which had already begun to rise on the second day, had reached 1·3 grm. nitrogen on the fourth day. The ammonia output remained above 1·0 grm. nitrogen until the twelfth day, but on the fourteenth or last day of the starvation experiment it fell to 0·73 grm. nitrogen. On the next two days, under the influence of Folin's starch and cream diet, the ammonia output fell to 0·52 and 0·35 grm. nitrogen; the uric acid output rose to 0·72 grm. on the first day, falling to 0·54 on the second day of the starch and cream diet. On the third day, with an ordinary purin-free diet, the uric acid output fell to 0·42 grm.

In Cathcart's experiment the uric acid output seems to bear the same relation to the acidosis, that we observed in our case. The rise in the uric acid output did not take place until after the ammonia output had risen, but it persisted for two days after the ammonia output had fallen to a normal amount. It may be explained on a hypothesis that the acidosis took twenty-four to forty-eight hours before it produced any effect, but, once established, produced an

increasing effect, which in Cathcart's case persisted for two days after the removal of the cause.

Consequently, in these three conditions in which the uric acid output is increased—severe diabetes, starvation, semi-starvation accompanied by high temperature—there is a common factor, e.g. the acidosis, and it is possible that the acidosis may have caused the rise in the uric acid output. But in these three conditions there is another common factor, i.e. the lack of carbohydrates, which may have been the cause of the increase in the uric acid. It is, therefore, not possible to answer the question definitely, but it seems probable that either the acidosis alone, or lack of carbohydrates alone, or both factors acting together may have produced this change.

The creatinine output was very constant, and only varied from 0·6 grm. to 0·52 grm. nitrogen. No rise took place on the temperature day. No creatine could be detected at any time.

TABLE X. *Experiment IV.*

Day of Expt.	Morning Period. 7 a.m.–3 p.m.			Afternoon Period. 3 p.m.–11 p.m.			Night Period. 11 p.m.–7 a.m.			Total N. of Periods.
	Vol. in c.c.	Grm. of N.	% of total N.	Vol. in c.c.	Grm. of N.	% of total N.	Vol. in c.c.	Grm. of N.	% of total N.	Grm.
6	242	4·34	28·7%	577	6·01	39·78%	977	4·76	31·5%	15·11
7	256	4·55	30·4%	608	5·96	39·81%	910	4·46	29·79%	14·97
8	275	4·11	29·07%	578	5·63	39·81%	810	4·40	31·12%	14·14
9	395	4·22	31·0%	548	5·95	43·7%	270	3·44	25·3%	13·61
10	215	4·18	29·44%	275	4·88	34·36%	547	5·14	36·2%	14·20

The diurnal variations in the nitrogen output were determined from the fifth to the ninth day of the experiment, and are shown in Table X, Diagram 8. The urine was again collected in three eight-hourly periods, i.e. from 7 a.m. to 3 p.m., 3 p.m. to 11 p.m., and 11 p.m. to 7 a.m. In this experiment the nitrogen excreted in the urine came partly from the daily wear and tear of the body, but chiefly from the nitrogen of the food. The meals were eaten with great punctuality in order not to alter the time at which the nitrogen would be normally excreted. On the sixth, seventh and eighth days the greatest amount of nitrogen was always excreted during the afternoon, and this is explained by the fact that the midday meal contained more nitrogen. The percentage amount of nitrogen excreted was remarkably constant, and only varied from 39·78 per cent. to 39·81 per cent. of the total nitrogen output.

The amount excreted during the morning period was also very constant, and only varied from 28·7 per cent. to 30·4 per cent. of the total nitrogen output; during the night period the nitrogen output was practically the same as in the morning period. It is of interest to note that, before the temperature day, the volume of the urine passed during the corresponding period of each day remained very constant.

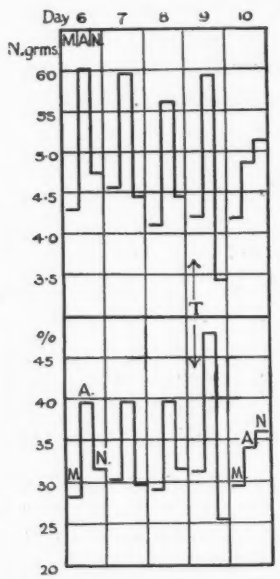
On the high temperature day the total nitrogen output in the urine for the twenty-four hours was decreased by 0·53 grm., and considerable alterations in the time of the nitrogen output occurred. In the morning period the nitrogen output was 0·11 grm. higher than on the preceding day, and the percentage rose from 29·07 per cent. to 31 per cent.; in the afternoon the nitrogen output was 0·32 grm. higher than on the preceding day, and the percentage rose from 39·81 per cent. to 43·7 per cent.; during the night a fall of 0·96 grm. occurred compared with

the corresponding period of the previous day, and the percentage fell from 31·12 per cent. to 25·3 per cent. The explanation of these changes is not very obvious, as two factors must have been concerned:

(1) The delayed metabolism of the proteins of the food, as in Experiment III.

(2) The diminution in the volume of the urine secreted during the bath period, as in Experiment II.

On both occasions in Experiment III the nitrogen output was decreased in the morning period, but increased in the afternoon period. The explanation suggested was that the metabolism of the food was delayed during the period of high temperature, and therefore less nitrogen was excreted in the morning period and more in the afternoon period. On both occasions in Experiment III very little urinary distress was felt, and the volume of the urine in the morning period was slightly diminished. The difficulty of applying the same explanation to this experiment lies in the fact, that more nitrogen was excreted during the morning period than usual, although the total nitrogen for the day was diminished. This, however, may perhaps be explained by the fact that considerable urinary distress occurred during the bath, and more urine was excreted than usual, and consequently, as in Experiment II, more nitrogen was washed out of the body during the morning period.



EXPERIMENT IV. DIAGRAM 8. The upper series of figures show the amount of nitrogen in grm. per 8 hours excreted in the urine during the three periods of the day: 7 a.m.–3 p.m. (M.), 3 p.m.–11 p.m. (A.), 11 p.m.–7 a.m. (N.). The lower series of figures show the percentage amount of the total nitrogen which was excreted in each period.

The diminution of the nitrogen output in the morning period owing to a delayed metabolism was therefore more than compensated for by the increased output due to the urinary distress. The fall during the night period was probably a compensatory process consequent on the extra amount of nitrogen excreted during the earlier part of the day.

On the day after the bath the total nitrogen output had risen to 14·2 grm., and was practically the same as on the day before the bath, i. e. the eighth day, so that it is convenient to compare the figures for the two days with one another. The nitrogen output during the morning period was 0·07 grm. higher than on the eighth day; in the afternoon period the nitrogen output was 0·75 grm. less than on the eighth day; in the night period it was 0·74 grm. higher than on the eighth day. These changes are probably caused by the great alterations in the volume of the urine, which were set up by the bath. The volume in the morning period was only slightly less than usual, but that of the afternoon period was very much diminished and probably accounts for the diminution in the amount of nitrogen excreted. During the night much more urine was passed than in the afternoon, although less than usual; and the rise in the nitrogen output is probably explained by this diuresis.

Discussion of Results.

Two factors have been suggested to account for an increase in the nitrogen output under the influence of high temperature:

(1) That the high temperature itself causes a destruction of the body proteins. This is the view advocated by Linser and Schmid (19).

(2) That the high temperature causes an increased energy production, and, in the absence of sufficient nitrogen free substances, the proteins are called upon to take a share in this energy production. This view is supported by F. Voit (40), whom we cordially thank for showing us his unpublished figures.

Our experiments were designed to test these two hypotheses. In the first two, a great excess of carbohydrate food was given in order to spare the protein metabolism as much as possible. In Experiment I the temperature was rapidly raised to 39·3° C., while in Experiment II it was more slowly raised, and maintained above 104° F. (40° C.) for 1¼ hours. As no increase in the nitrogen output occurred in either case, a temperature above 102·2° F. (39° C.) cannot have any destructive effect on the body proteins. The increased energy production caused by the high temperature must have been derived from nitrogen-free substances, and probably almost entirely from the carbohydrates.

In Experiment III the effect of the absence of carbohydrate on the protein metabolism was studied. An ample diet containing an excess of proteins was eaten, and a great retention of nitrogen in the body occurred. About 15 grm. of nitrogen were retained during the first two days of the experiment owing to the change from a diet containing a low protein content to one containing a great deal of protein, but the body was in nitrogen equilibrium at the time of the bath. A temperature over 102·2° F. (39° C.) was maintained for 3¾ hours, and a small rise in the nitrogen output of 0·66 grm. was observed. Before the second bath was taken 37 grm. of nitrogen had been retained, and a daily retention of 1·6 grm. was taking place. A temperature over 103° F. (39·5° C.) was maintained for two hours, and a rise of 0·51 grm. nitrogen was observed, but nevertheless 1·4 grm. nitrogen were retained on this day. These results do not necessarily mean that the high temperature caused a break-down of body proteins. A much more probable hypothesis is, that when an abundance of proteins was being eaten and retained in the body, some of the retained proteins took a small share in the increased energy production caused by the high temperature.

The nitrogen-free substances of the body must therefore have taken the chief share in the increased energy production, and the fat probably took a larger share than before, as the β-oxybutyric acid output was increased.

As a small rise in the nitrogen output occurred in Experiment III it was possible that a large rise might take place if, in addition to the deficiency of carbohydrate, the total caloric value of the diet was much reduced. Experiment IV was undertaken in order to test this view. However, the semi-starvation diet employed caused a considerable loss of nitrogen, and at the time of the bath the body was sparing its proteins as much as possible. A temperature of over 103·1° F. (39·5° C.) for 1¼ hours did not cause any appreciable rise in the nitrogen output, and consequently the high temperature did not produce any destruction of the body proteins. The whole of the increased energy production must have come from the nitrogen-free substances, and in this experiment the

great rise of the β-oxybutyric acid probably showed that the fat took a much larger share than in the other experiments.

These results are absolutely opposed to those of Linser and Schmid, who state that a body temperature well above 102·2° F. (39° C.) produces a rise in the nitrogen output. This conclusion of theirs is based on the results of six experiments in which the high temperature was produced by means of a Phoenix air-bath, and a rapid rise of mouth temperature always occurred.

It is suggested by Linser and Schmid, and by Mattes (23), that a rapid rise of this kind, taking place within an hour, is more likely to cause harm to the body than a more gradual rise.

In Experiment I of our series a body temperature of 102·7° F. (39·3° C.) was obtained within an hour after entering the bath. In the other experiments the steam was regulated so that it required over two hours to reach a temperature of 103·1° F. (39·5° C.). In none of these cases was an increase in the nitrogen output obtained, so that our experiments are opposed to this suggestion.

We have previously pointed out that the hot-air bath does not give a good representation of febrile conditions, as the surface of the skin is heated to a temperature much above the body temperature ; but it is very doubtful if such an explanation would account for the difference between Linser and Schmid's results and those obtained by us.

During their experiments a diet was given which was sometimes subject to variation throughout the long experiments in order to provide fresh acceptable food for the patients.

In two of their experiments with the patients Bl. and P. remarkable increases in the nitrogen output of 4·29 grm. and 2·65 grm. were obtained, but the authors themselves throw doubt on the reliability of their results, though it is difficult to accept their explanation, that this increase could have been brought about by the patients indulging in a larger amount of exercise than usual. In the case of the patient Bl. another great rise was observed, which is not explained at all by the authors.

The patient Szm. was heated to a temperature of 104·7° F. (40·4° C.) on one occasion, and to 104·4° F. (40·2° C.) on a second occasion.

During the first four days of the preliminary period of nitrogen equilibrium the nitrogen in the urine varied from 6·15 grm. to 8·23 grm. Then followed a period of three days during which the urine was analysed *en masse*, and the average (8·95 grm.) takes no account of daily variations ; on the next day 8·12 grm. were excreted. On the following day the bath was taken, and the nitrogen output was 9·52 grm. On the next two days the nitrogen output was 6·30 grm. and 7·54 grm. respectively. The second bath was then taken, and 9·55 grm. of nitrogen were excreted. On the next three days the amounts of nitrogen excreted were 6·68 grm., 8·81 grm., and 7·48 grm. respectively.

Although these figures seem to indicate a small rise on the days when the baths were taken, the analysis of three days' urine *en masse* makes the results rather inconclusive, especially as the excretion of nitrogen was very irregular on the other days of the experiment.

In the case of the patient L., the urine for three days at the beginning of the preliminary period of nitrogen equilibrium was again analysed *en masse*, and the average is given. The most striking fact about the experiment is that the highest nitrogen output (15·516 grm.) occurred two days before the bath, while the nitrogen output on the day of the bath (temperature 104·4° F. (40·2° C.)) was only 14·975 grm.

The two experiments, which were performed on Professor Linser himself, are also somewhat inconclusive.

In the first experiment the temperature was raised on three successive days. On the first day the nitrogen output was much the lowest in the whole experiment. On the second day it rose, and on the third day it reached a maximum. On the day after it slightly diminished, and here the experiment ended.

It might be suggested that the low value for the day of the first bath was due to a delay in the nitrogen excretion, but in none of the other experiments was this delayed nitrogen output obtained, not even in Professor Linser's second experiment. The uncertainty is still further increased by the fact that the experiment was only continued for one day after the bath.

Professor Linser's second experiment was complicated by the fact that carbohydrates were taken in large quantities, shortly before the day of the first bath, in order to test their effect in sparing the nitrogen metabolism. Such wide variations in the nitrogen output occurred, that it is difficult to say if the slight rise that took place on the day of the bath was not within the limits of these variations.

We do not consider that the evidence in Linser and Schmid's experiments, in favour of the hypothesis that a body temperature above 102·2° F. (39° C.) causes an increase in the protein break-down, is by any means as conclusive as many people have thought.

F. Voit concluded that the rise in the nitrogen output which he observed in dogs (after a high temperature lasting twelve and twenty-four hours) was only caused by the increased energy production set up by the high temperature, as he was able to prevent it entirely by giving excess of carbohydrate. In support of this view are the recent experiments of Hohlweg and Voit (15). These are based on the principle that when the disaccharide sugar maltose is injected subcutaneously into a dog, it is largely excreted in the urine. The authors raised the temperature of the dog for twenty-four hours, and found that much less maltose was excreted in the urine than before. This experiment showed that the animal had been able to use more of the maltose. In another series of experiments Hohlweg (14) injected maltose into a dog in the same way as before, and then subjected the animal to prolonged muscular work; again much less maltose was excreted in the urine. This latter series of experiments showed that the animal had utilized the maltose in order to supply the increased energy needs of the body set up by the hard work. Similarly, in the case of the dog with the raised body temperature the maltose must have been used for the increased energy needs of the body caused by the high temperature.

Other observers who have obtained similar results to F. Voit are Richter (32) and Formanek (8). Richter obtained an increase in the nitrogen output after a single prolonged period of high temperature. Formanek obtained a similar result after a series of short exposures.

In these cases the energy production must have been much increased, as the temperature was raised for a considerable length of time, and the rise of nitrogen may be explained on the hypothesis already discussed.

However, in cases where the high temperatures were of shorter duration different results have been obtained. F. Voit found that the rise in the nitrogen output in dogs, after a period of three hours, was much smaller than that which occurred after a period of twenty-four hours. Simanowsky (36), also working on dogs, found that after one hour no rise in the nitrogen output took place.

The conclusions to be drawn from our experiments agree with these results. In Experiment III the body temperature was over 102·2° F. (39° C.) for nearly $3\frac{3}{4}$ hours on one occasion, and for 2 hours on the second occasion; and on both occasions a small rise in the nitrogen output occurred. It is possible that, if the conditions could have been endured for longer, a larger rise would have taken place.

In Experiment IV the conditions were different, as owing to the loss of nitrogen during the previous week the body was sparing its proteins to the greatest possible extent. A body temperature of over 102·2° F. (39° C.) for $2\frac{1}{2}$ hours produced no rise in the nitrogen output; but, in this case, it is difficult to say whether a destruction of protein would have taken place, if the bath had been continued for a longer time.

The effect of high temperature on protein metabolism has always been investigated for the purpose of applying the results to fever.

The conditions of such experiments have differed from those of fever, in that the toxic action has not been present, and the individuals have been perfectly healthy.

However, they have resembled the conditions of fever, in that the high body temperature has been always associated with an increase in the production of energy.

Hitherto, in experiments on *man*, the question whether a rise in the nitrogen output might be due to the increased energy production, apart from the high temperature, has been very little considered. As we have pointed out, the only certain way of investigating the effect of high temperature alone is by giving an abundant supply of carbohydrate food, in order to cover completely the increased energy production. Experiments I and II of our series, in which these conditions were fulfilled, showed that no increase in the nitrogen output occurred. Consequently it may be concluded that, in fever, high temperature by itself does not produce any destruction of the proteins of the body.

Conclusions.

1. A rise of body temperature to 104·3° F. (40·2 C.) does not by itself cause any break-down of the proteins of the body.

2. If a diet of very high calorie value is taken, which contains a large excess of carbohydrate but a minimal quantity of protein, non-nitrogenous substances supply the whole of the increased energy production set up by the high temperature.

3. If a diet of ample calorie value is taken, which contains practically no carbohydrates but a large excess of protein, the fat metabolism is increased, but it is probable that the protein metabolism also takes a small share in the increased energy production set up by the high temperature.

4. If a diet of insufficient calorie value is taken, which contains practically no carbohydrates but a fair amount of protein, the fat metabolism is probably greatly increased, but the protein metabolism takes no share in the increased energy production set up by the high temperature.

We wish to thank Prof. Friedrich Müller for suggesting this subject to us, and for his constant help and advice.

REFERENCES.

1. Abderhalden und Bloch, *Zeitschr. physiol. Chemie*, Strassb., 1907, liii. 464.
2. Atwater and Bryant, cit. *Lusk's Science of Nutrition*, 2nd edit., Philadelphia, 1909.
3. Bornstein, *Berl. klin. Woch.*, 1898, xxxv. 791.
4. Camerer, *Zeitschr. f. Biol.*, Münch. und Berlin, 1901, xli. 271.
5. Cathcart, *Journ. Physiol.*, Camb., 1907, xxxv. 500.
6. Dunlop, Paton, Stockman, and Maccadam, *Journ. Physiol.*, Camb., 1897–8, xxii. 68.
7. Folin, *Amer. Journ. Physiol.*, 1905, xiii. 45 and 66.
8. Formanek, *Sitzungsber. d. k. k. Akad. d. Wiss., math.-nat.*, Wien, 1892, Abth. III, ci. 278.
9. Grafe, *Verhandl. d. Ges. deutsch. Naturf. u. Aerzte*, Abteil. f. inn. Med., 1911, Sept.
10. Gruber, *Zeitschr. f. Biol.*, Münch. und Berl., 1901, xlii. 407.
11. Haldane, *Journ. of Hygiene*, Camb., 1905, v. 494.
12. Haldane and Poulton, *Journ. Physiol.*, Camb., 1908, xxxvii. 390.
13. Hale White and Spriggs, *Journ. Physiol.*, Camb., 1900–1, xxvi. 151.
14. Hohlweg, *Zeitschr. f. Biol.*, Münch. und Berl., 1911, lv. 396.
15. Hohlweg und F. Voit, *Zeitschr. f. Biol.*, Münch. und Berl., 1908, li. 491.
16. Krehl, *Lehrbuch d. Path. u. Physiol.*, Leipzig.
17. Landergren, *Skand. Arch. f. Physiol.*, Leipz., 1903, xiv. 112.
18. Leathes, *Journ. Physiol.*, Camb., 1907, xxxiv. 205.
19. Linser und Schmid, *Deutsch. Arch. f. klin. Med.*, Leipz., 1904, lxxix. 514.
20. Lüthje, *Zeitschr. f. klin. Med.*, Berl., 1902, xliv. 22.
21. Lüthje und Berger, *Deutsch. Arch. f. klin. Med.*, Leipz., 1904, lxxxi. 278.
22. Magnus Levy, *Arch. f. exper. Pathol. u. Pharmakol.*, Leipz., 1899, xlii. 149; 1901, xlv. 389.

23. Mattes, *v. Noorden's Handb. d. Pathol. d. Stoffwechsels*, 2te Aufl., Berl., 1906–7, ii. 580.
24. May, cit. *v. Noorden's Handb. d. Pathol. d. Stoffwechsels*, 2te Aufl., Berl., 1906–7, i. 591.
25. Mörner, *Skand. Arch. f. Physiol.*, Leipz., 1903, xiv. 297.
26. O. Neubauer, *Deutsch. Arch. f. klin. Med.*, 1909, xcv. 211; *Verhandl. d. Kongr. f. inn. Med.*, 1910, 566.
27. Neumann, *v. Noorden's Handb. d. Pathol. d. Stoffwechsels*, 2te Aufl., Berl., 1906–7, i. 365.
28. V. Noorden, *v. Noorden's Handb. d. Pathol. d. Stoffwechsels*, 2te Aufl., Berl., 1906–7, ii. 89.
29. Friedrich Müller, *v. Leyden's Handb. d. Ernähr.-Therap.*, Leipz., 1897, i. 156.
30. A. Müller, *Centralbl. f. d. gesamte Physiol. u. Pathol. d. Stoffwechsels*, 1911, vi. 617.
31. Pembrey and Nicol, *Journ. Physiol.*, Camb., 1898–9, xxiii. 386.
32. Richter, *Virchow's Arch. f. path. Anat. u. Physiol.*, Berl., cxxiii. 118.
33. Rubner, *Arch. f. Anat. u. Physiol.*, Leipz. (Physiol. Abteil.), 1911, 39.
34. Schaffer and Coleman, *Arch. Internal Med.*, New York, 1909, iv. 538.
35. L. Schwarz, *Deutsch. Arch. f. klin. Med.*, Leipz., 1903, lxxvi. 233.
36. Simanowsky, *Zeitschr. f. Biol.*, Münch. und Leipz., 1885, xxi. 1.
37. Spiro, *Beitr. z. chem. Physiol. u. Pathol.*, Braunschw., 1907, ix. 481.
38. Sutton, *Journ. Pathol. and Bacteriol.*, Camb., 1909, xiii. 62.
39. Thomas, *Arch. f. Anat. u. Physiol.*, Leipz. (Physiol. Abteil.), 1909, 219.
40. F. Voit, *Sitzungsber. d. Ges. f. Morph. u. Physiol.*, München, 1895, 120.
41. Wolf, cit. *Lusk's Science of Nutrition*, 2nd edit., Philadelphia, 1909, 124.

STUDY OF A CASE OF DYSPITUITARISM

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With Plate 9

Part I.

As has been pointed out recently by Harvey Cushing (1), there are hardly any cases of pure hyperpituitarism or pure hypopituitarism. Both types are generally mixed; in other words, human pathology has mainly to deal with dyspituitarism. The changes brought about in the patients are manifold and interesting in more than one way: the growth of the skeleton, of the connective tissue in all parts of the body, and of the dermal structures is altered; metabolism, especially of fat and sugar, is seen to be disturbed; and various ductless glands, other than that which is the principal seat of the disease, are in the end affected by these troubles.

A case recently added to the Museum of the Royal College of Surgeons having been kindly entrusted to me for examination, for which my sincerest thanks are due to the Conservator of the Museum, I propose in this paper, after setting out certain less well-known facts as to the biology and pathology of the pituitary body, to give a detailed description of this case and briefly to discuss those questions upon which it will be seen to throw some new light.

In the glandular part, or pars anterior of the pituitary body which is developed from the ectodermal epithelium of the buccal cavity, two main categories of cells are distinguished: those of which the protoplasm contains granules and takes the ordinary stains—either eosin or haematoxylin—and those of which the protoplasm contains no granules and does not take those stains. The latter are called chromophobe or clear cells, the former, chromophil cells. These again are subdivided into oxyphil cells which take eosin, and basophil cells, which take haemalum or haematoxylin. The fact that there are intermediate states between the oxyphil and basophil cells justifies the belief that these two kinds of cells do not essentially differ from one another. Nor is anything known which would invalidate the theory that Rogowitsch's *Kernhaufen* (3) are exhausted chromophil cells. On the other hand, the changes which result from altered functions of the sexual glands tend to show that the chromophobe cells differ materially from the chromophil cells.

The pars nervosa or posterior is lined with epithelial cells which contain small granules and are derived from the ectodermal *Anlage*, the pars intermedia. The posterior lobe itself consists of loose neuroglial tissue. The

characteristic feature of these cells is that they contain pigment-granules. According to Kohn (5), they display a great metabolic activity, the lipoid pigment being probably a by-product of this process.

The histological appearance of the hypophysis varies at different periods of life (6 and 7). In the child's pituitary body, the cells of the pars anterior contain less glycogen, and the cells of the posterior lobe less pigment than they do in the later life; and the cleft between the pars anterior and the pars intermedia is wider than at the later period. The most striking changes, however, are noticed about the age of forty, when the basophil cells of the pars anterior are seen to bridge over, generally at three or four points simultaneously, the cleft between the anterior lobe and the pars intermedia, and thence to invade the pars posterior. It is about this period of life, too, that small adenomas are frequently met with, while before that time they are rare. These facts seem to indicate that the function of the pituitary body is not the same throughout life.

The sexual organs appear to be intimately connected with the hypophysis. During pregnancy, considerable enlargement of the gland takes place, primarily caused by the lessened function of the ovary. The enlargement is chiefly due to an increase in the chromophobe cells (7). This may go so far as to cause hemianopsia in pregnant women, and in a case described by Marek (9) even transient acromegaly and glycosuria were produced.

An enlargement of the hypophysis has been observed in castrated males, but in these cases it was due chiefly to an increase in eosinophil cells (10).

The way in which the pituitary body discharges at least one of its products shows its intimate relationship with the central nervous system. The cells of the pars intermedia produce hyaline bodies, which are found in the pars nervosa. Cushing and Goetsch (11) have satisfactorily established the correctness of the view first advanced by Herring (4), that these hyaline bodies pass through the loose connective tissue of the pars nervosa and, after there undergoing chemical changes which activate them in some way, enter the cerebro-spinal fluid of the third ventricle. The glandular part is generally believed to discharge its secretion either into the blood-stream direct (Cushing and others), or into the lymphatics (Edinger (12)). No certainty has yet been reached as to how many substances are produced by the pituitary body. The anterior lobe has so far resisted every attempt to isolate from it an active substance. Extracts of the posterior lobe are active and affect the heart, blood-vessels, kidneys, &c. in many ways. But whether these effects, which are found to vary according to certain circumstances, should be attributed to two different substances, or whether one substance is capable of producing them all, is a question still undecided (13 and 14).

Dyspituitarism is seen to influence the general development and growth of the body, the sexual organs, and certain metabolic processes. The changes in growth, such as occur in human pathology, are generally described by the name of acromegaly. They are said to consist mainly in an enlargement of the skeleton of the free parts of the body, i. e. the nose, lips, lower jaw, superciliary

ridges, hands, and feet. It is to be borne in mind, however, that not only the skeleton but also the connective tissue is subject to these growth-changes. It has long been known that the enlargement of the hands and the modification of their shape are almost entirely due to an increase in connective tissue. Arthur Keith (15) deduces from a study of the acromegalic skull that the pituitary secretion acts as a sensibilizator to the osteoblasts and causes them to react in an excessive degree to any strain put upon them. An increase and strengthening of bone will accordingly take place wherever bone-cells are stimulated. Keith considers this secretion to be of the nature of a hormone. The changes in the skull are readily explained by this theory. We shall see presently whether this explanation can also be applied to the changes in the other parts of the skeleton and the connective tissue.

Some authors have put forward the theory that acromegaly is a polyglandular affection (16). Others again hold that it is a constitutional disorder of growth, the assumption underlying both theories being that the pituitary tumour is not the cause of, but correlated with the growth-changes (17). The results of recent cases of surgical treatment, however, give strong support to Tamburini's view that it is the increased activity of the pituitary body which is the true cause of acromegaly. Harvey Cushing (18) has published photographs of his first successful case, which show a rapid and marked diminution of all the affected parts after partial removal of the pituitary tumour. Experimentally, it has not been possible, so far, to produce chronic states of hyperpituitarism (19), and the evidence from experimental sources is therefore very scanty. It is only in the paper by Crowe, Cushing, and Homans (20) that I have met with observations respecting growth-changes in experimental hypopituitarism. Those changes are described by the authors as being acromegaly reversed, i.e. shortening of the skull and diminution in the size of the limbs.

The close relationship between the pituitary body and the sexual glands has already been referred to above. The experiments of Crowe, Cushing, and Homans show that primary extirpation of the pituitary body leads to a marked decrease, and even to cessation of sexual activity. Unfortunately, the authors do not give details of the microscopical appearance of the sexual glands. All the experimental evidence is in favour of the view that lessened function of the pituitary body is the cause of these changes—a theory particularly well illustrated in the case of the dogs which Cushing subjected to partial removal of the anterior lobe. In human pathology, however, a tumour is found in cases of degenerative adiposogenitalis, as well as in cases of acromegaly. Whether the two components of Froelich's syndrome can be traced back to one and the same lesion seems open to doubt. In his most recent experiments, at all events, Cushing was able to show that the general adiposity may be due to posterior lobe deficiency also, whilst the sexual degeneration seems to be solely caused by lessened activity of the anterior lobe. This raises some interesting problems, as sexual degeneration, i.e. hypopituitarism, is generally, if not always, found to be associated with acromegaly, i.e. hyperpituitarism.

Recent inquiries have brought to light certain fundamental facts as regards the influence of the pituitary body upon metabolism. Loss of the pituitary body is followed by diminished metabolic activity. This is indicated by a lower temperature and, as Aschner and Porges have shown, by a decrease in the consumption of oxygen and in the output of carbon dioxide (Homans and Benedict). The proteid metabolism is diminished, and the same seems to be the case as regards the metabolism of sugar. It has been shown by Cushing and his colleagues that extirpation of the posterior lobe causes a higher degree of sugar tolerance, as indicated by the appearance of sugar in the urine. It seems, however, that the sugar taken in is not completely decomposed, as in normal animals, but is converted into fat and stored up in this form. It is also interesting to note that Aschner found in his dog a very low respiratory quotient, ranging from 0·658 to 0·708, when the animal was at rest. Although the metabolic activity is lessened by deficiency of hypophysis, there is a gain in weight due to the deposit of inert body fat. Few clinical observations are available as to the metabolism of anorganic substances, so that it is impossible to draw any definite conclusions from them; and as no chemical analysis could be made in the present case, it would serve no useful purpose to discuss this point here. To sum up: *Acromegaly is in all probability due to an excessive activity, whilst sexual infantilism, as also a general diminution of metabolism, is due to a deficient activity of the anterior lobe. On the other hand, deficiency in either the anterior or the posterior lobe produces adiposity.*

Part II.

Report on the case.[1]

1. *Clinical remarks.* This case is one of benign acromegaly. Nothing of the family history or previous diseases of the patient is known. He was born in 1869. Acromegaly was first noticed when he was 25 years old, in 1894, at which time he was a clerk in the City. The disease was fully developed two years later. In 1900, that is at the age of 31, he became bedridden, only getting up for a very short time every day. He died on January 28, 1911, aged 42, the immediate cause of death being probably heart failure. His mental abilities were good. He knew French and had taught himself German; he was fond of music and used to sing and play the violin. During the time he suffered from the disease he was frequently drowsy, and in the later stages was given to muttering to himself. He very often felt giddy, and for some years had frequent fainting fits, sometimes eight on one day. His sight was bad; so was his hearing, especially with the left ear; and his deafness was accompanied by the sensation of noises in the ear. His face was distinctly acromegalic, more so than his hands and feet. It is stated that during the last four years his hands and feet grew smaller again. The urine is said to have been normal throughout the disease. The body temperature and pulse were below normal, the temperature varying almost the whole time between 96·4 and 98, whilst the pulse was usually between 60 and 70, very rarely rising to 80.

2. *Post-mortem.* The patient measured after death 1,843 mm.; the trunk and face were disproportionally long, whilst the legs as well as the arms were

[1] The clinical notes were made by Mr. Frank Corner, who watched the case for over twenty years.

rather short, the arms again being relatively shorter than the legs. There was abundant fat in the subcutaneous tissue, and a lipoma was found beneath the skin near the left elbow above the m. triceps cubiti. Several pendulous fibromas issued from the skin, especially on the breast. The nipples were surrounded by a large pigmented area. The lower jaw was seen to be excessively developed, with the result that the lower incisors protruded beyond the upper ones when the mouth was closed. Both in the upper and in the lower jaw the teeth were not close together but separated by small interstices. The nose was large, the lips were thick, somewhat like those of a negro, the tongue was hypertrophied. The hair of the face was sparsely distributed, whilst the hair of the scalp showed no unusual features and was of normal thickness. The penis was smaller than normal, the free part being about 7 cm. long. The glans penis was covered by the praeputium. The testicles were small and soft, and the hair on the pubis scattered and thin; a distinct tuft of hairs being observable in each axilla. The hands were thick and broad, of the spatulate type. The hands, as well as feet, were not large relatively to the size of the body. It is, however, to be remembered, as above stated, that they were bigger some three or four years before death, and had diminished in size again.

3. *Skin.* A microscopical section of the skin of the chest showed an almost total absence of the papillae. The border between epidermis and cutis formed a nearly uninterrupted straight line. At a few points, however, the epithelium dipped down into the cutis. In some places these cones surround a patch of connective tissue. This intermingling of epidermal and cutical tissue, in itself unusual, appeared in a still more accentuated form in some instances, where the thin epithelial coat of a small protuberance in the skin was seen, in the microscopic section, to send down into the cutis different bands of epithelial cells, comprising from three to five layers. In the cutis these rows of cells formed a kind of network in which several islands of fibrous tissue were surrounded by epithelial cells. Towards the deeper parts of the cutis these epithelial layers bulged out so as to form a sort of flat papilla. This arrangement was met with in several places. (See Plate 9.)

As the skin was not quite fresh when prepared for microscopical examination, it is difficult to give any information of the stratum corneum, but it was apparently of normal thickness. The skin of the scalp showed nothing abnormal. There were numerous papillae. The hairs and glands were regular in form and size. The epithelial layer of the lip was thinner than normal. The cutical papillae were less numerous, so that, on the whole, the epithelium did not look as broken up as it does generally. In the tongue, too, the epithelium was not quite as thick as in a section of a normal tissue, although the difference was only slight.

The microscope showed that the thickening of the lip already referred to was principally due to hypertrophy of loose connective tissue. Judging from the curious tough consistency of the lips in living patients, Professor Keith suggests that there probably was a sort of mucous infiltration into the connective tissue.

4. *Pituitary tumour.* The tumour of the pituitary body had not only distended the sella turcica, but had protruded through the sellar diaphragm into the cranial cavity proper. All that could be found of the normal hypophysis was a small band of glandular tissue in one of the microscopical sections. The whole of the much distended sellar cavity was filled by the tumour. Both carotid arteries were surrounded by tumorous tissue. The right optic nerve was pressed upward and considerably flattened by the tumour, the left one could not be found at all. The skull showed, in the place of the sella turcica, a deep hole, divided by a nearly median ridge into a smaller right and a larger

left part. The floor of this cavity was irregular, being more worn away in some places than in others, so that a sort of network is formed. There was an open connexion between the sella and the nasal cavities. The sellar part of the tumour extended further to the left than to the right. The brain-cavity had been entered at two different points. Above the intrasellar part there was a round mass of the size of a big cherry connected with the sellar part by a short stalk. The growth had completely replaced the infundibular part of the brain and filled up the third ventricle. Superimposed on this solid tumour was a cyst of about the same size filled with colloid. Its wall was about 1 cm. thick. It reached right up to the corpus callosum, with the anterior half of which it was in contact. At the back it touched the optic thalamus. Independently of these two growths, a third had pushed its way from the side of the sellar part towards the mesial cortex of the right temporal lobe. This tumour was of almost cylindrical shape, about 1 inch broad and $1\frac{1}{2}$ inches long. It had excavated a deep hole in the substance of the brain, but was nowhere adherent to the nervous tissue. A large amount of colloid produced by the tumour was found in a subarachnoid cyst, situated at the base of the brain, between the temporal and frontal lobes, and extending a little way up into the Sylvian fissure. Whether this cyst was connected with the cystic part of the tumour described above cannot be stated with certainty.

As the post-mortem examination was performed forty-eight hours after death had occurred, the tumour was in an unfavourable condition for microscopical examination. No attempt was therefore made to demonstrate the nature of the granules by the use of Benda's more delicate stains. Nevertheless, it has been possible to establish certain interesting facts by relying on the haemalum and eosin stains. The protoplasm, having mostly undergone autodigestion, was generally not clear; the boundaries of the cells were faint, and the sections looked somewhat cloudy. In some places, however, the protoplasm had taken the stains well. Sections were prepared from different parts and numbered. Section 1 was taken from the intrasellar tumour, section 2 from the solid tumour in the third ventricle, section 3 from the cystic part, and section 4 from the tumour going into the temporal lobe.

As has already been mentioned, there was a rest of normal glandular tissue in section 1. It was a narrow band in one corner of the section; the stroma consisted of connective tissue and blood-vessels, mostly capillaries. In the spaces between the stroma were acini formed by glandular cells. There were abundant oxyphil cells; clear cells were scarce; *Kernhaufen* were seen in some places. There may have been also a few basophil cells, but the staining of these cells does not allow of a definite statement. The normal tissue turned abruptly into that of the new growth. In the tumour the cells were arranged, as it were, in columns. In section 1 these columns were generally divided by gaps, this being no doubt due to post-mortem changes. The centre of each column was occupied by a blood-vessel, of which the walls were exclusively formed by endothelial cells, and which must accordingly be regarded as capillaries. The tumour was built up mainly of round cells, of which the protoplasm was seen to be stained with eosin, only in some places a large number of bare nuclei, tightly packed together, were met with. These might be *Kernhaufen*. Some few giant cells were found. Their protoplasm was of a conspicuously dark-red colour in the stained section, and the number of nuclei they contained ranged from 2 to 7.

In section 2 hardly any trace of the architecture was left. Only in a few places could the arrangement of the cells around the capillaries be clearly distinguished, whilst in the greater part of the section only a few apparently damaged cells were scattered about. The cells were of the same type as those in the sellar tumour, although a little smaller. The great number of polynuclear cells was quite astonishing. It is a matter for consideration whether this might

not have been due to a post-mortem fusion of uninuclear cells. There were still other cells, the nuclei of which were irregular, situated on one side of the cells, and containing lumps of chromatin. This indicates an advanced state of autodigestion. Section 2 was, therefore, not reliable as to the structure of the tumour.

Section 3 was more decisive. The material was altogether more compact, and showed nothing of these advanced post-mortem changes. The structure of the wall of the cyst was the same as in the other parts of the tumour, with the sole exception, perhaps, that there were no giant cells. The cavity of the cyst was lined with cubic glandular cells; its colloid contents had taken the eosin stain.

Section 4 showed the same structure as the others. Polynuclear cells were frequent. This was the only section in which a larger blood-vessel had been cut. It remains to call attention to a curious observation: in the immediate neighbourhood of a sinusoidal capillary, there were thick clouds of small round cells with dense dark-staining nuclei and hardly any protoplasm. There was an almost complete absence of tumour cells from this region of round-cell infiltration. The real significance of this infiltration, which was entirely restricted to the neighbourhood of the sinusoidal vessel, is altogether obscure.

5. *Brain.* The cortex of the brain was of normal thickness. The convolutions were not flattened, the ventricles not noticeably dilated.

6. *Thyroid gland.* The thyroid gland was greatly enlarged. The microscope revealed changes which are almost unique. A portion of the follicles were distended, some measuring as much as 2 mm. in diameter; connective tissue formed broad patches and bands; and in some areas glandular cells were abundant and fairly closely packed together.

The distended follicles were filled with ordinary colloid, staining yellow with van Gieson's stain. The epithelial lining, especially of the smaller follicles, was seen in many instances to proliferate, so as to render the follicles in their appearance very similar to Graafian follicles with their discus proligerus. In some of the larger follicles the cubic epithelium was not continuous. It lined about half the circumference; in the other half it had partly disappeared, and partly been replaced by cells, of which the flat and elongated nuclei could clearly be distinguished. It was at least possible that these cells had been derived from the connective tissue. All the enlarged follicles had a fairly thick coat of fibrous tissue, which contained a large number of round cells with small and dark nuclei. These were evidently lymphocytes.

Two or three patches of connective tissue, each about two square centimetres, were seen in the microscopical section. They equally contained a comparatively large number of elongated nuclei and many lymphocytes. It was on the border of these patches that the epithelium of some of the larger follicles was missing. A few thyroid cells were observed in the middle of the fibrous patches. The broad bands of the tissue which divided the lobules represent the same histological features as the coating of the follicles. It may be assumed that the greater portion of the connective tissue was cicatricial tissue.

Those areas which were indicated above as being packed full with glandular cells were mainly built up of small follicles, most of which were round. Even the follicles which had been accurately divided equatorially showed a small lumen. They were filled with a substance which bore some resemblance to fresh fibrin, though it seemed to be of looser texture. This substance was certainly colloid. Among the large and light nuclei of the thyroid epithelium numerous cells with smaller and darker nuclei were scattered. Those, however, were probably not leucocytes, but may be taken to be older glandular cells. The general features of these areas might be said to resemble those observed in the thyroids of the foetus or of the new-born, and in Graves's disease.

7. *Other ductless glands.* The adrenal and parathyroid bodies were of normal size and structure. The pineal gland was not examined. The choroid plexus of the brain had undergone some autodigestion, but seemed to be normal.

8. *Testicles.* The microscopical examination of the testicle showed profound alterations both in spermatogenesis and in the interstitial tissue.

The fibrous walls of the seminiferous tubules were about three times as thick as normally. The elastic fibres were on the outer side and not increased in number. Their position showed that the wall had hypertrophied inwards. The epithelial cells within the tubules were not seen in their proper position in the section, as they were detached from the wall and formed clusters in the centre of the tubules. This, however, was probably a post-mortem change. The cells were cubic, and all presented the same features. No traces of spermatogenesis were met with anywhere.

The stroma was built up of loose connective tissue, in which some leucocytes were observed. In some places cells were found which were much bigger than connective-tissue cells. In the sections stained by van Gieson's method, their protoplasm took a straw-yellow, and the nucleus a dark-blue colour. The protoplasmic body was large and seemed to contain granules. The nucleus was small and dense. The conclusion is that we have here to deal with interstitial cells which have considerably diminished in number. The tunica albuginea was not thickened; it presented normal features.

9. *Larynx.* The larynx as a whole was not hypertrophied, the vocal cords were not longer than normally. No calcification had taken place in the skeleton. By means of the microscope an hypertrophy of the connective tissue in the submucous membrane and between the muscle fibres could be observed. The muscular fibres were pushed apart by the growth of the interstitial tissue. Around the glands the connective tissue was somewhat denser. The epithelial layer of the mucous membrane was apparently devoid of ciliated cells, even in the pocket of Morgagni. A lining of stratified epithelium was found in all places. The elastic fibres of the vocal cords were about twice as thick as in the normal larynx, and the epithelial layer of the vocal cords was also hyperplastic.

10. *Lungs.* Both lungs were short and had a broad base. The upper lobes were very small, the lower lobes constituting the bulk of each lung. On either side the first six ribs had produced deep impressions. These were most marked laterally, but could be traced on the whole of the convex surface of the lungs. The left lung rapidly widened downwards. Its free margins were pointed. Coal pigment was abundant in the lower, but scarce in the upper lobe, where the costal impressions were especially pale. The right lung had practically the same abnormal shape as the left one. From the anterior lower border of the middle lobe, a flaplike process projected downward. It became very thin towards the free margin, which was covered by the thick pleura visceralis, the anterior and diaphragmatic parts of which were joined together and projected still further downwards between the body-wall and the diaphragm.

A section taken from the upper lobe of the left lung showed slightly distended alveoli by the side of others which were collapsed; in other words, the lung at this point was partly emphysematous and partly atelectatic. The apex of the lower lobe of the left lung was entirely atelectatic.

Near the base of the left lung was some oedema; the size of the alveoli was normal. The flap springing up from the middle lobe was also examined. A thick layer of dense tissue had been formed in the pleura above the elastic band. This indicated a former pleurisy. The lung itself showed pronounced atelectasis. The alveoli were collapsed, their walls almost touched each other. Blood-vessels and smaller bronchi were frequently met with, and there was an

increase in connective tissue round them. Very little coal was deposited in this part of the lung.

11. *Digestive tract.* The tongue was considerably enlarged. This was partly due to a hyperplasia of the muscles and partly to an increase in interstitial tissue. The anterior part of the dorsum linguae did not deviate much from the normal condition, except that the fine pattern made by the grooves in the epithelial covering had become more coarse. There was only one well-developed circumvallate papilla on each side of the foramen caecum. Deep clefts divided the surface of the posterior part into a number of conoidal processes. These processes bore some resemblance to the papillae circumvallatae, but as they were not found in the characteristic position of those papillae, nor seen to be surrounded by a ridge, the resemblance was only superficial.

The pharyngeal tonsils were somewhat atrophied; their histological architecture was normal. The oesophagus also was normal. The relations of the abdominal viscera were profoundly altered. The greatest part of the left half of the abdominal cavity was occupied by the enormously distended sigmoid, which reached right up to the left dome of the diaphragm. Four coils of the jejunum were found in the left iliac fossa. The right half of the abdomen was filled by the small and great intestines, the stomach, and the liver. The transverse colon was filled with gas. The stomach was large, its walls were normal. The duodenum was enlarged and hypertrophied. The lymphatic tissue of the small intestine was considerably atrophied. Peyer's patches had disappeared, and the mucous membrane consisted of more or less dense connective tissue. The single bundles in the muscular coats were wide apart, the spaces between them being filled with loose connective tissue. The caecum was normal. A microscopical section of the appendix revealed the same striking absence of lymphatic tissue as was observed in the small intestine. The serous coat of the colon was slightly thickened. The walls of the rectum and sigmoid were hypertrophied to an extraordinary degree, the result no doubt of the chronic constipation from which the patient suffered. The muscular coat formed the bulk of the wall; the mucous membrane was only slightly hypertrophic.

12. *Glands of the digestive tract.* The parenchyma of the submaxillary gland had a normal appearance; only a slight increase in mucous cells was to be noted. The single lobes, however, were wider apart than those in the normal gland, the gaps between them being filled with loose connective tissue. This connective tissue seemed to be especially abundant around the blood-vessels and ducts, and in a few places was seen to protrude along these structures into a lobe. In these areas, too, there were more cells than in the rest of the connective tissue, so as to create the impression of a small and restricted round-cell infiltration. The areas were, however, extraordinarily small and very few in number. Around the intralobular ducts, too, the van Gieson stain revealed connective tissue. The changes in the submaxillary may be described as a primary but not very considerable hyperplasia of connective tissue.

The parotid gland also showed an increase in connective tissue. This went so far in some places that the interstitial tissue approximately equalled in breadth the glandular lobes themselves. The latter were not entirely composed of glandular parenchyma, i. e. acini and ducts. In many instances small patches and bands were met with, composed of cells, the protoplasm of which did not take any stain, whilst the nuclei were darkly stained with haematoxylin. They were long and narrow and slightly curved. The cell-borders were well seen. They showed the cells to be almost as big as an acinus, and round, except in so far as they had been slightly flattened by the pressure of neighbouring cells. They were fat cells and had probably developed out of degenerated glandular acini. If this be a correct diagnosis, the fact observed appears to be new, since there is, so far as I am aware, no record of any other example of fatty degenera-

tion of the salivary glands. The fact, however, that these fat cells are only seen within a lobe, and cannot be traced in the surrounding connective tissue, does not warrant the conclusion that fatty infiltration has taken place. The pancreas had been cut in the region of the tail. It was in an unfavourable condition for microscopical work. Only a few islands of Langerhans were seen in the section, but their scarcity may be accounted for by the locality whence the section was taken. It may be definitely asserted that the connective tissue had increased in volume. In most places it had only pushed the lobes wider apart, but at some points it had invaded the parenchyma, apparently replacing glandular tissue. In this way some lobes got split up into a number of fragments. There did not seem to be any fatty necrosis of the glandular cells.

The liver also was in a bad state of preservation. It was impossible to get good stains of the liver-cells: only the van Gieson sections which showed the distribution of the connective tissue were satisfactory. There was a marked increase in connective tissue, especially of Glisson's capsule. Within the liver lobes, the trabeculae of liver-cells were observed to be bordered on each side by fine threads of connective tissue, staining bright red in the sections. The architecture of the lobes was not altered, and we have therefore no right to speak of cirrhosis.

13. *Skeleton.* The skull showed the changes commonly met with in acromegaly. The cranial vault was thick, the sagittal and the parieto-temporal sutures were obliterated. The cranium was long and low. The mastoid process was exceedingly large; the upper temporal line had crept up a good deal, but not as much as in some other cases.

The lateral portion of the foramen jugulare was closed by a thin layer of bone. On the inner side, each of the sigmoidal sinuses ended in a cul-de-sac. On the outer side, a deep indenture with a solid bottom was seen, where normally the jugular vein pierces through the base of the skull. This blocking of the venous outflow had led to an excavation of the posterior wall of the petrous bone by the distended sinuses. The excavation was deeper on the right side, no doubt because the superior longitudinal sinus was connected with the right lateral one. A deep hole, found at the lateral end of the right sigmoid sinus, formed a forward continuation of the lateral sinus. On both sides the blood had escaped from the cranial cavity by an anastomosis which passed from the end of the lateral sinus through the wall of the cranium to a point just behind the mastoid process. This channel was wider on the right side than on the left.

The condyles were so much atrophied that, instead of protruding beyond, they were actually below the surface of the occipital bone. Their posterior parts were comparatively small and atrophied, and were furthest depressed.

The face showed a marked degree of prognathism. The nose was large, its root was not set back. The septum nasi deviated slightly to the left. The orbits were large and almost square. The condition of the lower jaw and of the teeth has already been referred to. It should be added that the ascending ramus of the mandibula was short as compared with the horizontal ramus. The chin was strongly developed. On the inner surface, the points of insertion of the genioglossi muscles and the grooves produced by the submaxillary glands were clearly seen. Owing to the size of the alveolar process of the maxillary, the hard palate was highly arched.

The spinal column showed a skoliosis to the left in the upper dorsal part, and to the right in the lower dorsal and upper lumbar regions. The cervical column was slightly longer in proportion to the other parts, this being mainly due to a thickening of the vertebral bodies themselves. The dorsal part was fairly proportionate to the total length of the body. The lumbar column was considerably lengthened, owing chiefly to a thickening of the intervertebral disks. These disks gradually thickened towards the promontory, so that the one

between the fifth lumbar vertebra and the sacrum was almost as thick as the body of the vertebra itself. The dorsal part showed an incipient lordosis; the lumbar part was straighter than usual. The sacrum and coccyx together formed almost a semicircle.

The thorax was barrel-shaped, a condition which is often observed in acromegaly and which is signalized by the low thoracic index. The three different parts of the sternum could easily be recognized: the manubrium and corpus were connected with each other by cartilage, and the xiphoid process was attached to the corpus in a similar manner. The whole sternum was twisted to the right, the jugular incision being in the middle line, the xiphoid process shifted about one inch to the right. Viewed from the side, the sternum was found to be in an exceptionally oblique position, its lower end projecting a good deal further to the front than the upper one. This caused a large antero-posterior diameter of the lower aperture. The corpus sterni was rather broader than usually found in males.

The first rib was flat and broad. The operculum of the thorax, which is formed by the first ribs of either side and the manubrium sterni, was higher on the right side than on the left. The second and third ribs described each a considerably wider curve than the one above it. Thus the thorax had reached its maximum width at the level of the third rib. The fourth rib was slightly drawn in, the fifth and sixth projected beyond the third, and the seventh had the same sweep as the third. The shape and position of the lower ribs were normal.

The pelvis exhibited many strikingly female characteristics. These were, however, restricted to the true pelvis, which might even be called ultra-female. The sacrum was broad and short; the greater sciatic foramen had a semicircular circumference and not an oval one as in males; the tuber ischii was bent outward, so that the transverse diameter was broader at this point than in the inlet. The pubic angle was obtuse and the symphysial cartilage broad. The inlet had a female shape; it was widest across the transverse diameter. The acetabula were turned more to the front than they generally are. The articulation surface was broad, and the incisura acetabuli was turned forwards and downwards instead of straight downwards, as is the rule. The wings of the iliac bones were bent upwards and the anterior-superior spines pointed inward.

Keith has shown that the acromegalic skull approaches in many ways the shape of the Neandertal skull. It is therefore of interest to note that, in the present case, the bones of the limbs also bore some resemblance to those found of the Neandertal race. The consideration of the detailed evidence for this statement, which is derived from a number of morphological observations, would lead us too far into the field of physical anthropology, but it is proposed to deal with this point exhaustively in a separate paper.

The bones of the proximal parts of the limbs were thick and had a clumsy appearance. The muscular attachments were well developed. In all the articulations the cartilaginous coats were hypertrophied. In the shoulder and knee-joints villi had protruded from the serous membrane into the articular cavity. The skeleton of the hand showed unmistakable signs of atrophy. Some of the carpal bones, especially the scaphoid and the semilunar, were deeply hollowed out. The metacarpals were flattened laterally. The grooves on the volar side of the first phalanges were deeper than normally, and bordered on either side by a sharp crest. It would appear as if the organism had economized as much in the matter of bone as possible without interfering with the function of the limbs. Analogous changes were met with in the feet, except for the tarsal bones, which were well developed. The shafts of the metatarsal bones, except the first, were flattened laterally. The heads of the bones were somewhat elongated towards the plantar side. If viewed from that side, they seemed to project knoblike downwards. The phalanges were thin, but not more so than is sometimes observed in normal skeletons.

A microscopical section was made near the proximal articulation surface of the humerus, at the point of attachment of the capsular ligament. The section had passed through the bone-marrow, spongiosa, compacta, and the tissue above the point where the ligament begins. The first thing to be noted was the extreme tenuity of the compacta as well as of the trabeculae of the spongiosa. A great deal of bone, therefore, must have been absorbed, although this cannot be demonstrated histologically. The thickening of the bone as a whole, on the other hand, showed that formation of new bone was also going on, and this could be seen under the microscope. In the mass of tissue constituted by the ligament, four distinct layers could be distinguished. There was, first, the osseous tissue proper, covered, secondly, by a much thinner layer, which was formed by evenly calcified cartilage. Above this, again, the tissue consisted, thirdly, of fibrous cartilage, which showed, scattered all over the section, smaller or larger patches of calcification. This gradually merged into the fourth layer, consisting of fibrous tissue.

The osseous tissue was of normal structure, with a ragged border marking the transition to the second layer. The second layer varied in thickness from one-half to one-tenth of that of the first. This layer had taken more haematoxylin than the bone; its upper border was an almost black line, from which faint dark streaks ran down towards the bone. This layer contained no vessels. The cells were for the greatest part true cartilaginous cells, but some of them, especially as observed under the high power lens, suggested some intermediate stages between cartilaginous and osseous cells. Their cavities were in some cases not regularly elliptical, but bulged out at one point. Other cells were elongated and thin, enclosed in cavities still more irregular, and, but for the lack of thin processes, might be called osseous cells. These intermediate forms were met with on the border between the osseous and the cartilaginous tissues. Multiplication of cartilage cells was frequent in the second layer. With few exceptions the cells were arranged in lines perpendicular to the surface. The general appearance of the third layer was that of fibrous cartilage. Numerous dark patches, however, generally somewhat elliptical in shape, were seen in this part. They contained either single or, more commonly, clusters of cells formed apparently by the proliferating of a single cell. The fourth layer was made up of ordinary fibrous tissue. The bone-marrow, it may be added, consisted of fat cells in this part of the humerus.

14. *Circulatory apparatus.* In the heart, hypertrophy of the left ventricle was the only pathological change. This, however, was not altogether a muscular hypertrophy, because the connective tissue also showed a remarkable increase. Long and fairly broad bands of connective tissue pervaded the myocardium. They were apparently connected with the vessels, for, when cut transversely, they were seen to contain a blood-vessel in the middle, and in those which had been cut longitudinally a blood-vessel, as a rule a smaller artery, could frequently be detected. These bands ran mostly at right angles to the muscular fibres, which ended abruptly on reaching the connective tissue.

The aorta was of normal appearance; it was not examined microscopically. The arteries of the limbs had extremely thick walls. This was chiefly due to hypertrophic changes in the intima, while the media was atrophied and arterio-sclerotic. In order to ascertain the thickness of the different coats, the elastic fibres can be used as landmarks. They are situated in the limb-arteries just beneath the intima, and everything inside them belongs therefore to the intima. In the popliteal artery of the present case, this coat formed the bulk of the wall. At one point it consisted of two layers, an outer one, which looked like ordinary fibrous tissue and which stained evenly bright-red with van Gieson, and an inner one, which showed numerous yellow specks. These two layers were held together by loose connective tissue, of which the fibres were partly red and partly yellow. About half an inch above the place whence this section was

taken, the inner layer came to an end, and the blood had partly flown into the tissue between the two layers. In a section taken from near this spot, the intima was formed by dense tissue, looking almost hyaline, which contained a great number of short fibres and many small cavities, so that it bore a superficial resemblance to fibrous cartilage. A narrow passage was left for the blood by the hyperplastic intima. At the outer border of the intima two elastic bands were seen for the greater part of the circumference. At one point, however, these split up, and numerous small elastic fibres were observed running obliquely to the other components of the arterial wall. They were short and thin and had the appearance of newly formed elastic tissue.

In the media patches of muscular tissue were seen in the central parts, of which the fibres had undergone necrosis. In some places deposits of lime had been formed near the outer border of the media. The bulk of this coat, however, consisted of fibrous tissue containing few nuclei except in the neighbourhood of the remains of the muscular tissue, where they were more frequent.

15. *Lymphatic glands.* An abdominal gland which was of ordinary size was examined microscopically. The first thing to strike the attention was a profound alteration in the architecture of the gland. A lymph gland has been aptly described as a gravel-filter, the follicles representing the larger pebbles in the bed of the filter being nearest the point where the lymph enters, whilst the proliferating centres near the outlet correspond to the finer sand. In the present case cortex and medulla could no longer be distinguished. Owing to an increase of the fibrous trabeculae the follicles were wider apart than normally. The follicles themselves were fairly full of lymphocytes: small round cells with dark-stained dense nuclei. No mitosis could be detected.

16. *Spleen.* The spleen had undergone but little change. The Malpighian corpuscles had diminished in number, but their finer histological appearance had not become altered. The blood-vessels had a very thick wall; the externa especially was much hypertrophied.

17. *Bone-marrow.* In a section of the bone-marrow, taken from the centre of the head of the humerus, sinusoidal, well-filled blood-vessels were seen. They were situated in a network of trabeculae, formed by round cells somewhat larger than leucocytes, and closely packed together. The spaces enclosed by these trabeculae were occupied by fat cells. The histological appearance seemed to indicate a revival of the production of leucocytes—which, in the young body, is the function of the bone-marrow.

18. *Muscles and nerves.* The striated muscles were increased in bulk, but this was solely due to an hypertrophy of the connective tissue within the muscles. The peripheral nerves and the sympathetic ganglia were greatly enlarged. Microscopical examination showed that this was an effect of an hypertrophy of the connective tissue of the nerve sheaths—similar to that observed in the muscles.

Part III.

Discussion.

(1) *Pituitary tumour.* The histological appearance of the pituitary tumour in the case under review strongly suggests, at first sight, that it is a malignant sarcoma. There is, however, a marked discrepancy between its histological appearance and its clinical behaviour. It is to be observed that the tumour had not invaded a single organ situated in its neighbourhood. The walls of the carotid arteries were intact, the optic nerve was seen to be flattened only owing

to the tumour pressing upon it, and the brain substance was in no way organically connected with the tumour. The changes in the shape of the sella turcica, and even the hole which had established a communication between the sellar and the nasal cavities, were also fully accounted for by the constant pressure of the growing tumour.

Doubts as to the sarcomatous nature of the tumour arise from the fact that its cells produced a colloid substance which, for all that can be made out, is the same as that produced by the normal glandular tissue. Although it so happened that sections prepared for microscopical examination in this case did not show the transitory stages between the normal glandular tissue and the tissue of the tumour, there are on record a number of cases of practically the same histological appearance where this transition could easily be demonstrated (24). In all these instances it was observed that the cells of degenerated adenomas of the hypophysis do not keep their epithelial appearance, but become smaller and assume a round shape. It may be inferred that the same development had taken place in the present case.

The conclusion, therefore, seems justified that the pituitary tumour in the present case is benign and of epithelial origin. I have in another place [1] suggested that tumours of this kind should be called round-cell adenomas.

The fact that a tumour which produces an excess of pituitary secretion is followed by symptoms of hypopituitarism as well as of hyperpituitarism has been explained by Cushing. His theory is that the pituitary cells produce two secretions, one of which enters the blood directly and causes acromegaly, whilst the other tends to approach the cerebro-spinal fluid without actually entering it, because the way is blocked owing to the pressure exerted by the tumour upon the infundibulum. The deficiency of this secretion in the general circulation thus brought about is the cause of Froelich's syndrome.

(2) *Testicles and thyroid.* Changes in the testicles and thyroid have frequently been found in cases of dyspituitarism.

In most cases where the testicles have been examined they have shown signs of lessened activity. Spermatogenesis was usually absent, and the interstitial cells were either rare or had entirely disappeared. The outer and the inner secretions are similarly hampered by dyspituitarism.

The histological appearance of the thyroid seems to vary very much in acromegaly. Some authors have reported cases showing colloid goitre, others observed a decrease in the size of the thyroid, and in a few cases changes somewhat similar to those found in the present case have been described. What, however, is important, is not so much to record the anatomical appearance of the thyroid, but to ascertain whether it corresponds with a physiological state of hypo- or hyperthyroidism. Now, if the colloid is the product of the internal secretion of the thyroid, then colloid goitre would mean that the body was unable to make use of the products of the thyroid, and that these, in consequence, were stored up in the follicles. Halsted first showed in grafting experiments

[1] These notes are to appear in the *B. M. J.* within a short time.

that the body only accepts the substances elaborated by the ductless glands if it actually wants them, and not merely when they are offered to it. It will be readily understood, moreover, that in other patients this inability of the body to make use of the thyroid products leads to atrophy of the gland. Lastly, the round-cell infiltration may be explained by analogy with the above-mentioned grafting experiments of Halsted. Just as these grafts are eaten up by leucocytes because they are not wanted, so the normal thyroid is destroyed in the end when its secretion cannot be made use of. It remains to account for the appearance in the present case of nodules of proliferating tissue. The fact that the size of the hands and feet diminished during the last period of the disease leads to the conclusion that the pituitary activity in the last few years was less than before. This in all probability affected the thyroid, and the proliferation of certain parts may well be the response of this gland to the altered conditions of the pituitary. *The different histological appearances of the thyroid are probably due to the same physiological fact: a lowered demand by the body-cells for the thyroid products.*

That the changes in the testicle and in the thyroid are in all probability due to hypopituitarism is shown by the detailed account given by Götzl and Erdheim (25) of a case of tumour of the third ventricle. This paper is now seen to form one of the most valuable contributions to our knowledge of dyspituitarism, although, at the time when it was written, the authors could not have anticipated this. For the paper is so far the only complete record of a case of pure hypopituitarism. Other cases of tumours of the third ventricle have unfortunately not been worked out from the same point of view. The tumour in Götzl and Erdheim's case is looked upon by the authors as a carcinoma, developed, in all probability, from the choroid plexus. It had filled up almost the whole of the third ventricle, and had thus blocked the way of the pituitary discharge into the cerebro-spinal fluid. The post-mortem also revealed an advanced atrophy of the testicle, combined with inflammatory infiltration of the interstitial tissue. The organ showed no signs of spermatogenesis, and no interstitial cells could be detected. In the thyroid the authors describe a colloid degeneration and round-cell infiltration, changes which seem to mark but an earlier stage of the distension of the follicles and the formation of cicatricial tissue found in the present case. *The observations recorded by the Austrian authors leave no doubt that the changes in the testicle and in the thyroid gland are due to a primary state of hypopituitarism.*

(3) *Skeleton.* The changes in the skeleton have often been said to be confined to the skull and the hands and feet. In the present case, however, as well as in the other skeletons which have been described in detail, changes were present in the thorax and pelvis as well as in the rest of the skeleton (26, 27, 28, 29).

The skeleton of the thorax must be considered with regard to its principal function, the respiratory movement. The shape of the thorax must be reflected in the lung, and the shape of the lung again must influence the moulding of the thorax. In order to explain the respiratory function, the ribs, according to

Keith (30), may be divided into four sets. The first rib stands by itself. Together with the manubrium sterni, it forms an operculum of the thorax, connected with the sternum by the sterno-manubrial cartilage. This operculum has an upward and downward movement, and simultaneously it expands and contracts. The second set comprises the second to the fifth ribs. They expand the upper lobe of the lung, the lower extremity of which corresponds roughly with the fifth rib. Each has a wider outward sweep than the one just above it, and the pleural cavity is thus made to expand upwards and outwards. The sixth to tenth ribs constitute the third set, which acts in connexion with the diaphragm upon the lower lobe. They move in much the same way as the ribs of the second set, but as they are set vertically one above the other they only allow the lung to expand in the antero-posterior and mesio-lateral directions. The last set, consisting of the eleventh and twelfth ribs, are part of the abdominal wall and do not participate in the respiratory function. The points of importance are that the respiratory movements of the ribs depend mainly upon their mutual position, and that the second and third sets of ribs correspond to the two principal lobes of the lungs.

In the present case we notice a diminution in the size of the upper lobe, and we find the fourth and fifth ribs, which normally belong to the second set, so shaped and situated that their function is assimilated to that of the third set, the dividing line between these two sets thus continuing to correspond to the fissura principalis of the lung. From this it may be inferred that the changes in the lung and in the thorax are correlated.

From the published drawings and photographs of the other acromegalic skeletons, especially from that of the interesting skeleton of Launois and Roy, it appears that they exhibited similar changes in the thorax, and it may be assumed that the lungs showed corresponding modifications, although this is not mentioned in the reports. That these changes are common in acromegaly is shown by the frequent mention of a barrel-shaped thorax. In the present case the cause may be assumed to be the hypertrophy of the sigmoid and rectum. These parts have pushed the other contents of the abdominal cavity upwards against the domes of the diaphragm, which was thus prevented from drawing the lungs effectively downwards. Consequently, those parts of which the ventilation depends chiefly upon this movement, namely, the upper lobe and the portion of the lower lobe which is drawn into the complementary spaces, became more or less atelectatic. We find, indeed, that the upper lobe was partly atelectatic, and that the flap depending from the middle lobe was very markedly so. The middle part of the lung, on the other hand, more filled with air than usually, pressed upon the lower ribs of the second set, i. e. the fifth and fourth, in an upward direction, and caused them to assume the shape now seen in the skeleton. The corresponding shifting of the fissure between the two lobes may, at least partly, be accounted for by the atelectasis in the upper lobe and the distension during the respiratory movements of the greater part of the lower lobe.

Besides the present case, a female pelvis in a male acromegalic subject has

been observed by Launois and Roy and, judging by the illustration, was present in the cases of Buday and Janesco, and of Thomson. I have elsewhere (31) offered some suggestions concerning the mechanics of the pelvis, and have tried to show how the female pelvis is moulded by mechanical forces. These act upon the symphysis pubis, the sacro-iliac joint, and the acetabula, and if the bone cells become hypersensitive excessive growth will occur at these points. This will cause the acetabula to move outwards and thus broaden the pelvis, making it approximate more nearly to the female type.

It is safe to say that the growth-changes in acromegaly are not confined to particular parts of the body, but that they occur everywhere, and that their degree, in accordance with Keith's theory, depends upon the intensity of the stimuli acting upon the different parts.

(4) *Influence of the ductless glands on growth.* It is not only the pituitary body, but almost all the other ductless glands as well, that seem to have an influence on growth. The pineal body retards development; the thyroid, the adrenal bodies, and the sexual glands seem to promote it. No embryological theory, however, seems so far to have taken this into account. The nature of the influence of the ductless glands must be taken to be chemical. That the chemical relations between the various organs play an important part in determining the growth of the body has been exhaustively shown by Richard Hertwig (32) in his theory of biogenesis. This author, however, does not treat of the leading part played by the glands of internal secretion. The fact that their activity does not come into play until some time—about four months—after development from the fertilized egg, because it is only at this period that they are anatomically developed, acquires special interest in the present connexion. It may indeed be said, from this point of view, that the whole of the intra-uterine development may be divided into two periods: (*a*) from the fertilization of the egg to the time when the ductless glands begin to function, and (*b*) from that time onwards up to birth. Development, however, continues in later life, where three periods at least can be distinguished. The first begins with birth and ends at the time when the sexual functions first make their appearance. This revolution in the system, as it may rightly be called, at least in the female, has probably been prepared by gradual changes in the other ductless glands, among which the pineal body seems to play a foremost rôle, and ceases to function when the testicles or ovaries begin to do so. Towards the end of the sexual period other changes in the ductless glands are observed, such as have been described above in the case of the hypophysis.

From the point of view of our present knowledge of the ductless glands the writer ventures to suggest that the most urgent problems are those raised by the question of the interrelation of the various members of this family at the different periods of life above referred to, and the formulation of some working hypothesis as to the nature of the influence exercised by those bodies on cellular metabolism. This, however, is a matter which more properly concerns the department of physiological chemistry.

Conclusions.

The principal points of importance which emerge from a collocation of the published materials, and some of which seem to deserve special attention in the light of the foregoing discussion, may be briefly summarized as follows:

1. There are hardly any cases of pure hyperpituitarism or of pure hypopituitarism, but both types are generally mixed.

2. Sexual infantilism and adiposity are symptoms of hypopituitarism and are generally, if not always, found associated with acromegaly, i.e. hyperpituitarism.

3. This would be accounted for by Cushing's theory that one secretion enters the blood directly, whilst the way for the other to the third ventricle is blocked by the pressure from the tumour upon the infundibulum.

4. The changes in the histological appearance of the thyroid in cases of acromegaly are probably due to the same physiological fact: a lower demand for the thyroid products on the part of the body-cells.

5. The changes in the thyroid and in the testicles are due to a primary state of hypopituitarism.

6. The growth-changes in acromegaly are not confined to particular parts of the body, but occur in all parts of the skeleton.

7. These growth-changes are, according to Keith, explained by the assumption that the secretion of the pituitary body acts as a hormone, which renders the osteoblasts more sensitive to mechanical and other stimuli.

It was an honour and sincere pleasure for me to be allowed to prepare this paper in constant communication with Professor Arthur Keith, and I desire to take this opportunity to express my deepest gratitude for the valuable help he gave me in more than one way. Professor Harvey Cushing, of Baltimore, has kindly sent me his valuable papers on the hypophysis and on dyspituitarism. My thanks are further due to Mr. H. K. Wilson, who prepared the microscopical sections, and to Mr. Finerty, who specially contrived a number of measuring instruments, which materially assisted my work on the skeleton. I have also to thank Dr. Frank Corner for placing the clinical notes of this case at my disposal.

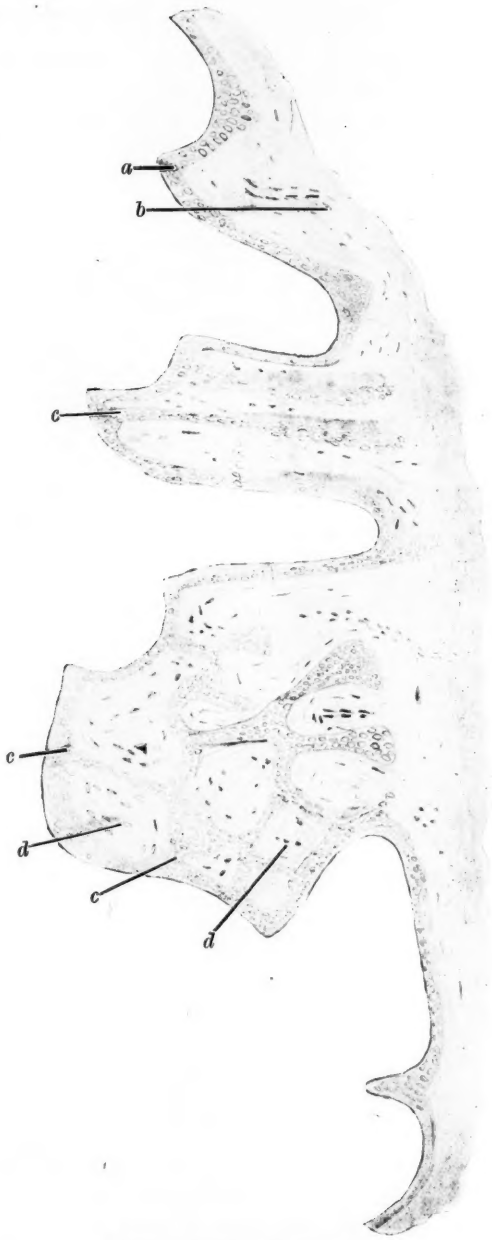
REFERENCES.

1. Cushing, Harvey, *Harveian Lectures*, 1911, 31.
2. Schäfer, *Quain's Anatomy*, 11th edit., Lond., 1912, part 2.
3. Rogowitsch, *Zieglers Beitr. z. path. Anat.*, Jena, 1889, 453.
4. Herring, *Quart. Journ. Exp. Phys.*, Lond., 1908, i. 151.
5. Kohn, *Arch. f. mikr. Anat.*, Bonn, 1910, lxxv. 337.
6. Erdheim, *Zieglers Beitr. z. path. Anat.*, Jena, 1903, xxxiii. 158.
7. Thom, *Arch. f. mikr. Anat.*, Bonn, 1901, lvii. 632.
8. Erdheim u. Stumme, *Zieglers Beitr. z. path. Anat.*, Jena, 1909, xlvi. 1.
9. Marek, *Gynäk. Zentralbl.*, 1911, 1612.

10. Fichera, *Il Policlinico*, Roma, 'sez. chir.', 1905, xii. 250, 299, 319.
11. Cushing and Goetsch, *Amer. Journ. Physiol.*, 1910–11, xxvii. 60.
12. Edinger, *Arch. f. mikr. Anat.*, Bonn, Festschr. f. Waldeyer, 1911, lxxviii. 496.
13. Schäfer and Vincent, *Journ. of Physiol.*, Lond., 1899, xxiv. Proc. 19.
14. Schäfer and Vincent, *ibid.*, 1899–1900, xxv. 87.
15. Keith, *Lancet*, Lond., 1911, i. 993.
16. Sternberg, *Nothnagels Spez. Path. u. Therapie*, article Acron.
17. Strümpell, *Deutsche Zeitschr. f. Nervenheilkunde*, Leipz., 1897, xi. 51.
18. Cushing, *Annals of Surgery*, 1909, 1003.
19. Exner, *Deutsch. Zeitschr. f. Chir.*, 1910, cvii. 172.
20. Crowe, Cushing, and Homans, *Johns Hopkins Hosp. Bull.*, Baltimore, 1910, xxi. 127.
21. Aschner and Porges, *Biochem. Zeitschr.*, Berlin, 1912, xxxix. 200.
22. Benedict and Homans, *Journ. of Med. Research*, Boston, 1911–12, xxv. 409.
23. Goetsch, Cushing, and Jacobson, *Johns Hopkins Hosp. Bull.*, Baltimore, 1911, xxii. 165.
24. Benda in *Flatau und Jacobsohns Handbuch der Nervenkrankheiten*, Band II.
25. Götzl und Erdheim, *Zeitschr. f. Heilkunde*, 1905, xxvi.
26. Buday und Janesco, *Deutsch. Arch. f. klin. Med.*, Leipz., 1898, lx. 385.
27. Thomson, H. A., *Journ. Anat. and Physiol.*, Lond. and Edinb., 1890, xxiv. 475.
28. Geddes, A. C., *ibid.*, 1911, xlv. 256.
29. Launois et Roy, *Études biologiques sur les Géants*, Paris, 1904.
30. Keith in *Recent Advances of Physiology*, vol. ii, edited by Leonard Hill.
31. v. Borin, *Anat. Anz.*, 1912, xli. 590.
32. Hartwig, Oscar, *Allg. Biologie*, Jena, 1909.

DESCRIPTION OF PLATE.

a, Epidermal epithelium.
b, Cutis and subcutaneous tissue.
At *c*, *c*, the epidermal epithelium is seen to dip down into the cutis.
d, *d*, Islands of fibrous tissue, surrounded by epithelial cells.



Section through skin of breast

THE FRAGILITY OF THE RED BLOOD CORPUSCLES[1]

By G. G. BUTLER

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Introductory.

WHEREAS our knowledge of the pathology of the white blood corpuscle is extensive, that of the red blood corpuscle is much more limited: this is to be expected since the structure of the white corpuscle is more varied and its changes more obvious than in the red cell. The more recent advances of knowledge in the pathology of the red blood corpuscle can be ascribed to the phenomenon of haemolysis, the great interest of which is due to the part played by haemolytic agents present in disease, where there is evidence that the red corpuscle varies in the ease or difficulty with which it loses its characteristic colour. It is possible to attribute the escape of colouring matter to an altered state of the corpuscle or to a diminished or increased fragility of these to laking influences. There are many laking substances or haemolytic agents too numerous to enumerate in detail; it suffices to mention that those haemolytic agents produced in disease and known as specific haemolysins have been investigated to the greatest extent.

Records on the resistance or fragility of the red blood corpuscles to specific haemolysins are meagre and it apparently is similar for the simplest of haemolytic agents.

My object was to investigate the fragility of the red blood corpuscle as shown by haemolysis with weak solutions of sodium chloride, with the idea that the behaviour of the red cell under these conditions might throw some light on their pathology, and that some insight into those diseases characterized by blood destruction might be furnished.

Does the corpuscular fragility vary in disease? Do the methods of collecting and preserving blood alter the fragility in any way? What is the corpuscular resistance of the red corpuscle in physiological saline? for it is in this medium, free from any interference on the part of the plasma, that the red corpuscle is frequently investigated. These are but a few questions that need answering.

The term 'fragility' is convenient and encompasses the fact that the red corpuscle varies in resistance, shown in the way it gives up its haemoglobin.

[1] A thesis presented for the degree of M.D. in the University of Cambridge.

[Q. J. M., Jan., 1913.]

French writers use the word 'resistance'. I shall use the terms resistance and fragility synonomously.

One of the earliest references to corpuscular resistance appears in a paper by Ribierre, where he states that he puts trust in this saline test as a measure of corpuscular fragility. The subject is again alluded to by Chauffard in an investigation of a case of congenital jaundice. In a paper on the estimation of the tonicity of different sera by the lowering of the freezing-point, Hamburger states that the corpuscular resistance to haemolysis is a more delicate method of attaining this end, arguing that the results are more easily observed and that the salt solutions with which he works take a part in the normal life of the organism. The strength of this argument cannot be denied and enhances the value of any observations that may be made on corpuscular fragility towards salt solutions.

More recently this subject has been investigated in special diseases such as pulmonary tuberculosis, scarlet fever, and various types of jaundice and anaemia. Peyton Rous has compared the resistance of normal and pathological red cells against a specific haemolysin and against weak salt solutions. The effect of repeated haemorrhages on fragility towards salt solutions has been investigated by Theobald Smith. Bramachari has observed that some red cells of human blood are more resistant to hyposmotic sodium chloride solutions than others. Sutherland and McCay have investigated the alteration of resistance brought about by ingestion of certain salts. Feuillié has suggested that the corpuscular resistance should be investigated, not only of blood as such, but also of red cells free from plasma, but he gives no results. It is on the lines just stated that the present investigation has been pursued, and there appears to be an opportunity of working out the subject more fully and to bring together a somewhat scattered knowledge of the subject.

Description of Methods.

Various methods have been employed in the investigation of the corpuscular fragility, but the following may be noted with advantage:

(*a*) *Ribierre's method.* This was the first satisfactory method advocated. A stock solution of 0·5 per cent. sodium chloride is made, though stronger solutions are sometimes found necessary. A series of small glass test-tubes of about the same dimensions is then set up in a row on a stand: into the first fifty drops of the 0·5 per cent. solution are placed, into the second forty-eight drops of the solution and two drops of distilled water, into the third are placed forty-six drops of the saline solution and four drops of distilled water; other tubes are filled in similar fashion, two drops of the sodium chloride solution being replaced by two drops of distilled water in each succeeding tube. Now into each of these tubes are placed two drops of 'diluted' blood and the tubes gently shaken: haemolysis, if it is going to occur, takes place at once and readings can be taken almost immediately. Chauffard favours this method.

(*b*) *Hamburger's method.* The apparatus used in this method is similar to

Ribierre's, except that each glass tube in which the blood and salt solution is mixed is drawn out into a carefully calibrated capillary tube. Into the tubes are placed 2 c.c. of saline solution, each tube containing a weaker saline solution than the preceding tube: and then into each tube is placed 0·05 c.c. of defibrinated blood. Further procedure is now identical with Ribierre's method.

(*c*) *Dudgeon's method.* Here a standard 1 per cent. solution of sodium chloride is prepared. On the lower end of a capillary pipette (as described by Wright) is placed a fine mark to indicate the length of the capillary tube to be used as a standard unit of volume; the standard unit of volume is thus that volume of fluid which the marked off portion of the capillary pipette will contain. A series of unit volumes can then be drawn up into the pipette, each volume separated from the next by a small bubble of air. By taking up one volume of 1 per cent. sodium chloride solution and nine volumes of distilled water into this pipette, a 0·1 per cent. solution of sodium chloride is obtained: by taking two volumes of 1 per cent. sodium chloride and eight volumes of distilled water, a 0·2 per cent. solution is obtained. Progressively stronger solutions of saline can be made readily, and as each dilution is prepared the mixture is blown into a miniature test-tube made from a small piece of glass tubing sealed at one end. A series of tubes containing progressively increasing strengths of saline solution is thus set up. The thumb is then pricked, blood is obtained and drawn up into the capillary pipette in columns as in the case of saline solution and distilled water. A sufficient number of volumes being obtained, one volume is placed into each tube of saline solution, the mixture is gently shaken and then allowed to settle down, when haemolysis, if present, is readily detected. This method is an excellent one when dealing with such wide differences of strength as 0·1 per cent.: for finer differences in strength such as 0·475 per cent., 0·45 per cent., and 0·425 per cent. not only is it necessary to prepare other standard dilutions, but even then half volumes are found necessary; this allows many opportunities of error to occur.

Many objections are apparent in the above-described methods. Chauffard uses a constant dilution of blood, namely 1 in 25, and a fairly constant total volume throughout his experiments, but his unit of volume is a drop, a notoriously inaccurate measure. Hamburger uses a constant total volume and a constant dilution of blood, namely 1 in 40; but he uses defibrinated blood, against which there are obvious objections. The difficulty of detailed work in Dudgeon's method I have already pointed out. In one method we have a dilution of 1 in 25, in another a dilution of 1 in 40: defibrinated blood is used in one, fresh blood is used in another, so that there is no basis for accurate comparison. For the satisfactory investigation of this subject it cannot be too important to work with recognized standards and dilutions. I have used a 1 in 10 dilution of blood throughout the investigation, and, further, the red cells were examined not only as blood, but also freed from plasma and suspended in normal saline solution.

Technique employed.

Kahlbaum's pure sodium chloride has been used in making up all solutions, and all solutions have been renewed daily. Three solutions were made up to commence with:

A 1 per cent. solution of sodium chloride. (100 c.c.)

A 0·85 per cent. solution of sodium chloride. (100 c.c.)

A mixture of 0·85 per cent. sodium chloride and 0·85 per cent. sodium citrate. (100 c.c.)

In order to prepare the desired dilutions of saline solution, the following procedure is carried out:

Two well calibrated burettes are taken and washed with the solution which they are to contain, one is filled with the 1 per cent. solution of sodium chloride and the other with distilled water. Examples of the method of obtaining the dilutions are given:

To prepare a 0·3 per cent. NaCl solution, mix 3 c.c. of 1 per cent. NaCl with 7 c.c. of distilled water.

To prepare a 0·325 per cent. NaCl solution, mix 3·25 c.c. of 1 per cent. NaCl with 6·75 c.c. of distilled water.

To prepare a 0·35 per cent. NaCl solution, mix 3·5 c.c. of 1 per cent. NaCl with 6·5 c.c. of distilled water.

To prepare a 0·375 per cent. NaCl solution, mix 3·75 c.c. of 1 per cent. NaCl with 6·25 c.c. of distilled water.

To prepare a 0·4 per cent. NaCl solution, mix 4 c.c. of 1 per cent. NaCl with 6 c.c. of distilled water.

The solutions are allowed to run from the burettes and mix in small glass bottles which possess air-tight stoppers. We are thus provided with 10 c.c. of freshly prepared solutions of sodium chloride of different strengths in well-stoppered bottles, upon each of which can be marked the strength of the salt solution it contains.

For the actual experiment capillary pipettes are made, but with a finer bore than those described by Wright. The broad end of the capillary pipette is fitted with a rubber teat, and at a convenient distance from the end of the capillary portion a fine transverse line is marked with a glass writing pencil: the portion thus marked off is conveniently about two-thirds of an inch in length, and represents the unit standard of volume on which the experiment is to be performed. One of the bottles of standardized salt is then taken and a series of nine columns of the fluid is withdrawn from it into a capillary pipette, each column corresponding accurately in length to the unit marked on the pipette, and each column separated from the next by a bubble of air. These columns of fluid and air bubbles are drawn into the wide neck of the capillary pipette, where they mix, and the air bubbles got rid of; a continuous column of salt solution, representing the nine columns combined, may now be driven down the capillary portion and its length marked on the pipette. This done, the saline

solution is blown into a miniature test-tube made from glass tubing ¼ inch in bore and 1½ inches in length, sealed at one end by being drawn out in a flame so as to form a slightly tapering extremity. The process of measuring the nine volumes of each other solution can now be carried out rapidly and easily, for this amount is marked on the capillary pipette. It is scarcely necessary to note that the capillary pipette is washed with a little of the saline to be used in order to remove any of the previous saline solution that may be clinging to the pipette. A series of small tubes is thus set up, each containing nine volumes of salt solution of known strength. The thumb of the patient is cleaned and then encircled at its base with an elastic band to cause engorgement. By pricking the thumb close to the nail-bed with a surgical needle a good flow of blood is obtained, and a series of columns of blood may now be drawn up into the capillary pipette, each column of blood being accurately measured by the unit standard of volume marked on the pipette. The first two columns of blood drawn up are not used in the experiment, for they are contaminated with the remains of the salt solution left in the capillary pipette. The requisite number of columns are taken into the pipette and then one column is injected into each of the miniature test-tubes. Gentle shaking at once mixes the blood with the saline solution. The miniature test-tubes are then placed aside for a short time in order to allow the mixture they contain to settle down before observations on the extent of haemolysis are recorded. If necessary, gentle centrifugalizing will complete the sedimentation. It should be noted that in the experiment so performed there is a constant dilution of blood to the extent of 1 in 10.

The most likely source of error occurs at the stage of measuring nine small volumes of saline solution. However, this is only performed once in the examination of any blood, so that the error, if it occurs, is a constant one and identical for each dilution of saline solution. This, I think, compares favourably with the other methods where for every dilution of saline solution used there is a source of error, and probably a very variable one.

The estimation of the extent of the haemolysis in the experiments has been made entirely by the depth of tints, and the following terms have been employed:

Complete haemolysis—when no red deposit is observable.

Marked haemolysis—when the red tint is marked and yet there is a red deposit of cells remaining.

Distinct haemolysis and trace of haemolysis applying to less deep tints.

Some experimenters have prepared standard solutions of haemoglobin for each blood they have examined: estimates of the percentage of haemoglobin set free at each dilution of the series being made by comparison with the standards prepared with known percentages of blood in distilled water. This involves an increase in volume of blood to be obtained from each patient examined. There is sufficient difficulty in obtaining blood even in small quantity from the average patient, that there is advantage in any method which obtains constant results with the smallest amount of blood possible.

During this investigation I have found it quite obvious when haemolysis commences and there is ease in noting changes in tint for each strength of saline solution. Objections may be raised against this method of estimating haemolysis. There is no fixed point at which all the red cells are haemolysed, for at a certain dilution only the least resistant cells are haemolysed, and more and more cells are haemolysed as the solutions become weaker. So that the naked-eye method of estimating haemolysis only notes at what percentage strength haemolysis commences or is complete and does not estimate when the majority of the red cells are haemolysed. On the whole, it appears more reasonable to judge the resistance of a blood by its weakest members rather than the more resistant. Most interesting results would be obtained by estimating what percentage strength of saline would cause the majority of red cells to haemolyse, but it is difficult to see what further light they would throw on the subject, and that at a great increase in difficulty of technique.

In the description above, the resistance of the red corpuscles in blood was examined. For the preparation of washed red corpuscles the following procedure is carried out:

Blood is obtained from the thumb engorged by a constricting india-rubber band, and is allowed to drop into a small glass centrifuge tube filled with citrated saline solution. After every three or four drops are obtained the constricting band on the thumb is removed in order to ensure the blood obtained being well oxygenated, at the same time the centrifuge tube is inverted several times to allow thorough mixing of the blood and anticoagulant. The constricting band is then reapplied to the thumb and further drops of blood obtained; a total of fifteen or twenty drops is, as a rule, necessary. The tube is then centrifugalized at a low speed, the red cells are deposited, and then the supernatant fluid is pipetted off and replaced by normal saline (0·85 per cent. NaCl). Two additions of normal saline will be found sufficient to wash away completely all citrate and plasma. The complete procedure may now be summarized:

1. Make the main saline solutions, 1 per cent. NaCl, 0·85 per cent. NaCl, and citrated saline solution.

2. Make the finer dilutions, usually 0·475 per cent. to 0·3 per cent. NaCl.

3. Measure out nine volumes of each dilution into the miniature test-tubes, which are then marked and set up in a stand.

4. Three-quarters fill a centrifuge tube with citrated saline.

5. Obtain the blood to be examined, and determine fragility of the red cells in blood and as washed red cells.

Certain advantages, I think, may be claimed for the method used:

1. All solutions are made up fresh daily.

2. A rapid and easy method of preparing solutions with small percentage differences, and at the same time these dilutions are made up in sufficiently large volume to prevent error.

3. Each solution is made up as a daily stock solution, so that results are more comparable than if fresh solutions are made up for each experiment.

4. Experiments are carried out expeditiously.

5. A constant dilution of the blood to 1 in 10 is used.

6. Blood is examined in as undisturbed a state as possible, and in the case of the washed red corpuscles there is less interference by using citrated saline than by defibrination by whipping.

A. *The Fragility of the Red Corpuscle in Health.*

1. *Fragility of the red corpuscles in blood.* Here the fragility of the red corpuscle is examined while it still remains in plasma, and hence in as normal a condition as possible.

The blood is obtained from a puncture in the thumb and is rapidly drawn into a capillary pipette and then examined before any clotting can take place. My own blood I have examined on very many occasions, for it has invariably been used as a control. The extent of haemolysis of red blood corpuscles occurring in certain strengths of sodium chloride is given for five healthy adults; the terms 'complete', 'marked', 'distinct', and 'trace' referring to the extent of haemolysis observed in the tubes. Here, as elsewhere, the dilution of blood employed is 1 in 10.

NaCl %	*Adult male.*	*Adult male.*	*Adult male.*	*Adult male.*	*Adult female.*
0·300	complete	complete	complete	complete	—
0·325	marked	marked	complete	complete	—
0·350	marked	marked	marked	marked	marked
0·375	distinct	distinct	trace	marked	distinct
0·400	trace	trace	0	trace	trace
0·425	0	0	0	0	0
0·450	0	0	0	0	0

With one exception haemolysis just begins in 0·4 per cent. sodium chloride solution.

In the case of my own blood haemolysis commences in 0·4 per cent. NaCl in about 80 per cent. of observations, while in 20 per cent. it commences in 0·375 per cent. saline solution. The observations on my own blood have been very nearly daily for a period extending from November, 1909, to March, 1910, inclusive, during the earlier part of which the lower figures were chiefly obtained. The point of commencing haemolysis of the red cells in normal blood may then be taken as being extraordinarily constant, and that in terms of sodium chloride they may be stated to have a resistance of 0·375 per cent. to 0·4 per cent. when examined in a 1 in 10 dilution.

There appears to be a definite diminishing grade of tints or extent of haemolysis to be observed in the results of the experiments: from complete haemolysis in weak saline solutions we pass to a trace of haemolysis in stronger solutions. If we examine the deposited cells in the tubes, it will be found that in those tubes with the least amount of haemolysis the majority of cells still contain their haemoglobin: while in those tubes showing a considerable amount of haemolysis only a few of the red cells remain unhaemolysed. If haemolysis towards weak saline solutions is purely a physical phenomenon, and if all red

cells are of a similar resistance, then we ought to observe that at a certain definite dilution all the red corpuscles should be haemolysed to the same extent. As this is not observed, I think it is reasonable to assume the varying fragility of the red corpuscles in blood to be the cause of the graduation in extent of haemolysis rather than give up the opinion that haemolysis by hypotonic salt solution is a physical effect until definite proof is obtained against this.

To the conclusion, then, that the normal resistance of the red corpuscle in blood is somewhere between 0·375 per cent. and 0·4 per cent. of sodium chloride should be added the statement that these figures only represent the resistance of the weakest red cells in the blood. Maximal resistance will be that strength of saline solution which haemolyses all the red cells in a blood. Maximal resistance is a very difficult phenomenon to be sure of, and not so easily observed as commencing haemolysis, and further would be of less value to investigate, for it is more important to judge a blood by its weakest members than by the more resistant.

(*a*) *The importance of a constant dilution.* In the above remarks on the haemolysis occurring with normal blood it was carefully noted that the experiments were performed with a dilution of blood to 1 volume in 10. The importance of this will be seen on examination of the following table, where the effect of varying dilutions is noted:

Dilutions. NaCl %	1 in 5.	1 in 6.	1 in 8.	1 in 10.	1 in 12.	1 in 20.
0·300	complete	complete	complete	complete	complete	complete
0·325	marked	marked	marked	marked	complete	complete
0·350	marked	marked	marked	marked	marked	marked
0·375	trace	trace	distinct	distinct	distinct	distinct
0·400	0	0	trace	trace	trace	trace
0·425	0	0	0	0	0	trace

Assuming for the time being that the percentage salt concentration of the blood in question is 0·85 per cent. in terms of sodium chloride, or, in other words, that the blood is isotonic with 0·85 per cent. NaCl, we can work out the percentage of sodium chloride in each tube where haemolysis commences.

For the 1 in 5 dilution a trace of haemolysis has resulted from the addition of 1 volume of 0·85 per cent. NaCl (which we have assumed is isotonic with blood) to 4 volumes of 0·375 per cent. NaCl, and this mixture has a percentage strength of 0·47 per cent. sodium chloride. Similarly working out the other cases, we find the final saline percentage to be as follows:

Dilutions.	1 in 5.	1 in 6.	1 in 8.	1 in 10.	1 in 12.	1 in 20.
NaCl	0·47 %	0·454 %	0·456 %	0·445 %	0·44 %	0·446 %

These figures indicate a fairly constant result, and also indicate the accuracy with which commencing haemolysis can be detected. From the whole observation we may infer that commencing haemolysis of the red cells in blood varies with the dilution in which they are examined, and hence the necessity of definitely stating the dilution employed in order that the fragility of red corpuscles may be compared. Both numerically and practically a 1 in 10 dilution

is found useful, and further in this dilution haemolysis is easily detected in its earliest stages.

Finally, then, when red corpuscles are examined as blood and in a dilution of 1 in 10 the minimal resistance may be stated to vary between 0·375 per cent. and 0·4 per cent. NaCl, and more usually the higher figure; the maximal resistance under the same conditions being between 0·3 per cent. and 0·325 per cent. sodium chloride.

Variations in the fragility of the red cells during the course of the day have not been very extensively observed; in those cases where I have examined my own blood during various hours of the day there has not been any appreciable variation in the resistance.

(*b*) *Results compared with those of other observers.* Limbeck has given 0·46 per cent. NaCl as the minimal resistance. Hamburger, using defibrinated blood and a dilution of 1 in 40, gives 0·54 per cent. NaCl. Chauffard in his first paper gives the figure 0·46 per cent. NaCl when using a dilution of 1 in 25; according to his second paper he uses 'drops of blood' and a dilution of 1 in 70, and obtains 0·46 per cent. to 0·42 per cent. saline as figures for commencing haemolysis, and 0·16 per cent. NaCl for complete haemolysis. Ribierre has given 0·42 per cent. sodium chloride and 0·44 per cent. sodium chloride as representing the minimal resistance. Bramachari uses blood and a dilution of 1 in 2, and gives the figure 0·29 per cent. for commencing haemolysis, complete haemolysis being obtained at 0·19 per cent. sodium chloride. Christophers and Bentley, using normal blood and a 1 in 6 dilution, find 0·449 per cent. NaCl gives the minimal resistance. Hutchison and Panton give 0·4 per cent. sodium chloride for commencing haemolysis when 1 in 11 dilution is employed.

These results are rather discordant, but can be explained if we take into consideration the varied methods and dilutions employed.

2. *The fragility of washed red corpuscles.* The next step will be to examine the corpuscular fragility, not in the form of blood, but of the actual red corpuscle freed from any interference on the part of the plasma. The procedure for collecting and washing the red corpuscle has already been described.

Below are given a series of examinations conducted on my own washed red corpuscles, and in order that they may be compared with the fragility of the red corpuscle in blood itself, observations under the two conditions are given side by side. The dilution employed is again 1 in 10.

W. R. C. = Washed red corpuscles.

NaCl %	Blood.	W. R. C.	Blood.	W. R. C.
0·300	complete	complete	complete	complete
0·325	marked	complete	marked	complete
0·350	marked	marked	marked	marked
0·375	trace	marked	distinct	marked
0·400	0	marked	trace	marked
0·425	0	trace	0	distinct
0·450	0	0	0	trace
0·475	0	0	0	0
Date	1/1/10		17/1/10	

NaCl %	Blood.	W. R. C.	Blood.	W. R. C.
0·300	complete	complete	complete	complete
0·325	marked	complete	complete	complete
0·350	marked	marked	marked	marked
0·375	distinct	marked	distinct	marked
0·400	trace	marked	trace	marked
0·425	0	distinct	0	distinct
0·450	0	0	0	0
0·475	0	0	0	0
Date	16/2/10		3/3/10	

Experiments performed on widely different dates have been chosen purposely, and in no case has a wider been observed than in the examples shown above. The resistance of the washed red cells is here shown to vary between 0·425 per cent. and 0·45 per cent. of sodium chloride solution, and experiments on several normal individuals give similar results. As in the case of blood itself, the effect of varying dilutions should be noted, and a table showing this is now given.

Extent of dilution of washed red corpuscles employed.

NaCl %	1 in 5.	1 in 6.	1 in 10.	1 in 15.	1 in 20.
0·350	marked	marked	marked	marked	complete
0·375	marked	marked	marked	marked	marked
0·400	trace	marked	marked	marked	marked
0·425	0	trace	distinct	distinct	distinct
0·450	0	0	trace	trace	trace
0·475	0	0	0	0	0
Total salt concentration at point of commencing haemolysis.	0·49 %	0·496 %	0·49 %	0·477 %	0·47 %

These results show a slight variation in fragility of the red corpuscles in different dilutions, but if we work out the total salt concentration in each dilution for the point of commencing haemolysis we find that the apparent variation in the fragility is dependent on the final salt concentration. The figures are not found identical in any case, it is true, but the error for 1 in 5 and 1 in 6 dilutions is larger than could occur with the higher dilutions. In the case of the 1 in 10 dilution, haemolysis has commenced at 0·45 per cent. NaCl, which is the highest concentration at which haemolysis has ever occurred in my own blood; if we take the other extreme, 0·425 per cent. NaCl, for the commencing point of haemolysis—and it does more frequently occur there—we get a total salt concentration of 0·467 per cent. NaCl, which is practically the same as the figures given for the higher dilutions of 1 in 15 and 1 in 20, where the error is likely to be less.

From the examination of the last two groups of results we may come to the conclusion that the minimal resistance of washed red corpuscles is represented by the figure 0·425 per cent. to 0·45 per cent. sodium chloride if the corpuscles are used in a 1 in 10 dilution.

By comparing the fragility of red corpuscles as blood with the fragility

of washed red corpuscles we find that there is a difference; the former is less than the latter, but as a rule this difference is never more than 0·05 per cent. in terms of sodium chloride. If 0·85 per cent. sodium chloride solution is isotonic with blood, and if haemolysis by weak saline solutions is purely dependent on osmotic tension differences, then the point at which haemolysis commences in the case of blood and of washed red corpuscles in 0·85 per cent. sodium chloride should be identical, but is not borne out experimentally. How can this difference be accounted for? Two explanations may be entertained: 1. That the isotonic value of blood in terms of sodium chloride is not 0·85 per cent. NaCl. This, I think, may be dismissed at once, for there is abundant evidence that 0·85 per cent. NaCl is isotonic with blood. 2. That the red corpuscles have been injured or left unprotected in some way by the process of washing, haemolysis by weak saline solutions still being dependent on differences in osmotic tension, but now acting on an injured or unprotected red corpuscle.

To elucidate this matter the following series of experiments were performed, the red corpuscle fragility being examined under the following conditions: 1. As blood itself. 2. As red corpuscles in citrated plasma—blood being collected in citrated saline solution, centrifugalized, and the red corpuscles examined. 3. As red corpuscles washed in citrated saline to free from plasma. 4. As in 3, but the red corpuscles have been replaced into the citrated plasma again. 5. As red corpuscles washed in 0·85 per cent. saline. 6. As in 5, but the red corpuscles have been replaced into citrated plasma again. 7. As in 5, but the red corpuscles have been replaced into citrated saline solution again.

NaCl %.	Exp. 1.	Exp. 2.	Exp. 3.	Exp. 4.	Exp. 5.	Exp. 6.	Exp. 7.
0·325	marked	marked	marked	marked	complete	marked	marked
0·350	marked	marked	marked	marked	marked	distinct	marked
0·375	distinct	marked	trace	trace	marked	trace	marked
0·400	trace	trace	trace	trace	marked	trace	distinct
0·425	0	0	0	0	distinct	0	trace
0·450	0	0	0	0	trace	0	0
0·475	0	0	0	0	0	0	0

It will be noticed that the fragility of the red corpuscles has remained identical whether examined as blood or as red corpuscles in citrated plasma and in citrated saline. The removal of the plasma in the third experiment by simply washing the red corpuscles in citrated saline solution has not affected their resistance, and apparently red corpuscles in citrated saline solution behave as normal. On washing the red corpuscles with 0·85 per cent. NaCl their fragility has been increased, but the normal fragility is recoverable by simply replacing them into citrated plasma again, and this also applies if they are replaced into citrated saline solution, but the recovery is not so complete.

These experiments have elucidated the matter to this extent that the increased fragility of the washed red corpuscles in 0·85 per cent. NaCl is not a permanent injury, at all events for the first hour after the washing has taken place.

It appears to me that the explanation is more satisfactorily given by lack of

protection as the result of removal of some substance or substances from the immediate neighbourhood of the red corpuscles. With the opinion that possibly the albumin of plasma normally protects the red corpuscle, an experiment was undertaken with the object of estimating the value of a foreign colloid as a protective agent for the red corpuscle.

A thin emulsion of starch was made, and the fragility of washed red corpuscles was estimated in the presence and absence of this emulsion.

NaCl %.	1	2	3
0·300	complete	complete	marked
0·325	marked	marked	marked
0·350	marked	marked	marked
0·375	marked	marked	distinct
0·400	distinct	distinct	trace
0·425	trace	trace	0
0·450	0	0	0

1. Red corpuscles washed in 0·85 % NaCl.
2. Red corpuscles washed in thin starch emulsion made with 0·85 % NaCl.
3. Red corpuscles in citrated plasma.

The results obtained show that starch emulsion has no power of protecting the red corpuscle from haemolysis by hypotonic solutions even to a slight degree, but this crude experiment scarcely warrants the statement that plasma does not afford some protection. It will have been noticed also that the fragility of the red corpuscle in citrated saline solution with and without plasma is identical and an apparent contradiction set up. Possibly the explanation rests in the proposition that the distribution of ions in an albuminous fluid must be very different to that in a simple fluid, but it is politic not to venture unnecessarily into a question which is extraneous to this paper though intimately connected with the subject.

Other observers' results. It will be well to record and compare here the results of other observers on the fragility of the washed normal red blood corpuscle, though it is but recently that the red corpuscle has been examined free from interference on the part of the plasma.

Peyton Rous in 1909 examined the red corpuscles washed with 0·9 per cent. NaCl and, using a dilution of 1 in 3, says haemolysis commences in 0·46 per cent. to 0·42 per cent. saline and is complete at 0·35 per cent. Tileston and Griffin give the figures 0·44 per cent. and 0·36 per cent. for beginning and complete haemolysis. Chalier, using Ribierre's method and a dilution of 1 in 70, states 0·44 per cent. saline just causes haemolysis for washed red corpuscles. These results differ a good deal, but the more recent observations conform nearly with my figures, 0·425 per cent. to 0·45 per cent. sodium chloride when using a 1 in 10 dilution.

3. *The effect of keeping washed red corpuscles in normal saline.* This is another question that requires answering. Any change in resistance as a result of keeping will be an indication of alteration from the normal state, and any experiment performed on red corpuscles at such a time after withdrawal of the blood cannot be considered to have been performed on normal red corpuscles.

For this investigation red corpuscles were collected into citrated saline in the ordinary way and then washed twice with 0·85 per cent. sodium chloride. The fragility of these cells was then examined at definite hours and compared later with the resistance of cells kept in the citrated saline just as they were collected, and hence with plasma present as well.

NaCl %.	1 hr.	2 hrs.	3 hrs.	4 hrs.	18 hrs.	22 hrs.
0·325	marked	marked	marked	marked	marked	marked
0·350	marked	marked	marked	marked	marked	marked
0·375	marked	marked	marked	marked	marked	marked
0·400	distinct	distinct	distinct	distinct	distinct	marked
0·425	trace	trace	trace	trace	distinct	marked
0·450	0	0	0	0	trace	marked
0·475	0	0	0	0	trace	marked

NaCl %.	48 hrs.	NaCl %	60 hrs.
0·325	marked	0·5	marked
0·350	marked	0·600	marked
0·375	marked	0·700	distinct
0·400	marked	0·725	distinct
0·425	marked	0·750	distinct
0·450	marked		
0·475	marked		

Interesting results are obtained here. It will be noticed that the fragility of the washed red cells, examined every hour after withdrawal, remains unaltered for four hours. At the eighteenth hour a change is noticed: the fragility apparently is greater than what it was, and becomes more marked at the twenty-second hour and forty-eighth hour, when, curiously, the haemolysis appears to be identical in each strength of saline solution (up to 0·475 per cent. NaCl) into which the red corpuscles are placed. At the sixtieth hour haemolysis appears uniformly in whatever strength sodium chloride is employed, up to a certain degree, and if this result is traced higher it is found that even in 0·75 per cent. sodium chloride there is very distinct haemolysis. If the red corpuscles are kept longer than this in the normal saline it will be found that haemolysis will even begin in that solution. Possibly the red corpuscle is so injured by the washing and being forced to live in a comparatively non-nutritious medium that its whole existence and chemical stability is altered, or possibly even its life is slowly destroyed, so that it behaves as an inert body giving up during haemolysis a certain proportion of its haemoglobin purely as a chemical solvent action on the part of the water. Beyond this I have no explanation for the phenomenon, but whatever the explanation the observation remains, that the red corpuscle which is allowed to remain in contact with normal saline solution alone soon loses its normal fragility.

McNeil has obtained results which vary considerably from mine on this question of the fragility of washed red cells after being kept in normal saline. He finds that in a normal individual 80 per cent. haemolysis is shown in 0·42 per cent. NaCl at three hours, while after this only 9 per cent. haemolysis is obtained in this percentage strength of saline; and in one other case he finds

70 per cent. haemolysis at two hours and only 16 per cent. at four hours; in other words, the fragility of the red corpuscles has decreased by being kept in normal saline solution. I cannot think the explanation he gives is correct, that 0·85 per cent. NaCl is hypertonic for blood corpuscles, and that the decreased fragility to 0·42 per cent. is due to the red cells adapting themselves to this hypertonicity. I can say, however, that the results in my own cases have been repeatedly observed, and that, far from decreasing in fragility, the washed red corpuscles after a certain time rapidly increase in fragility if kept in physiological saline solution.

In the next table is given the results of keeping red corpuscles in citrated saline solution in which plasma is present; in other words, just as blood was collected into citrated saline solution.

Red corpuscles in citrated saline—plasma present.

NaCl %.	1 hr.	18 hrs.	24 hrs.
0·325	marked	marked	marked
0·350	marked	marked	marked
0·375	distinct	marked	distinct
0·400	trace	trace	trace
0·425	0	0	0
0·450	0	0	0

The above table shows the results for my own blood, but the resistance has not been determined later than twenty-four hours after withdrawal. In another case (adult female) the resistance at fifty-one hours was practically identical with the resistance of my red corpuscles at twenty-four hours. A striking difference is noticed at once when comparing this result with that for the washed red cells.

Red corpuscles, after being kept in citrated saline just as they were collected, retained their normal resistance to salt solution even at twenty-four hours.

4. *The effect of obtaining blood under pressure on the fragility.* It has been the usual method to obtain blood from the thumb engorged by means of a constricting rubber bandage, so that a short investigation was undertaken to compare the fragility of the red corpuscles obtained under pressure and direct from a vessel. Unfortunately, I have met with difficulty in obtaining blood from a normal individual except while under an anaesthetic, and in the following cases blood was obtained from healthy patients undergoing trivial surgical procedure under light chloroform or ether anaesthesia.

NaCl %.	Blood from cut vessel.	Blood from engorged thumb.	Washed red corpuscles. Blood from cut vessel.	Washed red corpuscles. Blood from engorged thumb.
0·325	marked	marked	marked	marked
0·350	marked	marked	marked	marked
0·375	distinct	distinct	marked	marked
0·400	trace	trace	trace	distinct
0·425	0	0	trace	trace
0·450	0	0	0	0
0·475	0	0	0	0

It appears, then, that there is no appreciable difference in the fragility of the red corpuscles obtained under the two conditions, and further, this statement

applies whether the red corpuscles are examined as blood or as washed red corpuscles.

5. *The effect of various anticoagulants on the fragility.* It has already been noted that the red corpuscle obtained by collecting blood into citrated saline solution has the same fragility as the red corpuscle examined as blood. The conclusion is that citrated saline solution is a satisfactory means of preventing coagulation, for it does not alter the corpuscular fragility towards weak salt solutions. Now as regards sodium oxalate solution: Blood was received into a tube of 1 per cent. sodium oxalate and then centrifugalized, the red corpuscles were then washed twice with 0·85 per cent. salt solution, and the resistance towards weak salt solutions tried.

NaCl %	Blood itself.	Oxalated blood washed in 0·85 % NaCl.	Citrated blood washed in 0·85 % NaCl.
0·325	marked	complete	complete
0·350	marked	marked	marked
0·375	distinct	marked	marked
0·400	trace	marked	marked
0·425	0	distinct	distinct
0·450	0	trace	trace
0·475	0	0	0

The result obtained with citrated and oxalated blood is identical. There does not appear to be any disadvantage in either method of preventing coagulation from the resistance point of view. Some authors, I should state here, have observed alterations in resistance as the result of using oxalate solution. Widal, Abrami, and Brulé have tried the effects of various anticoagulants. They have collected blood into potassium oxalate, sodium fluoride, sodium citrate, and leech extract, and having washed the red corpuscles twice with 0·9 per cent. NaCl, have obtained identical results in all cases. My own experience with oxalate and citrate solutions confirms these observations, but my single experience with leech extract gave unsatisfactory results, haemolysis occurring more easily in the blood collected into leech extract than in blood examined as such.

NaCl %.	Blood.	Blood and leech extract, healthy adult.	Blood and leech extract, another healthy adult.
0·325	complete	complete	complete
0·350	marked	complete	complete
0·375	marked	marked	marked
0·400	trace	marked	marked
0·425	0	distinct	distinct
0·450	0	0	0
0·475	0	0	0

The leech extract was used in these experiments in extremely small quantity, but sufficient to prevent coagulation.

The red corpuscle fragility has distinctly increased in both cases as the result of using a minute portion of leech extract. The effect of defibrination by whipping by oxalate and fluoride of sodium on red corpuscle fragility has been investigated by Iscovesco, who states that even after twice washing with normal

saline the fragility towards the same haemolytic serum differs with each method employed.

6. *The effect of oxygen on the corpuscular fragility.* Oxygen plays such an important part in the life of the organism and comes into such intimate relation with the red blood corpuscle itself that it is but natural to inquire into the effect it has on normal fragility. I cannot find any reference on this question and hence imagine it has escaped the observation of other investigators.

A difficulty at once is encountered in dealing with blood as such, for coagulation sets in too quickly to allow the fragility to be tested. It has, therefore, only been possible to experiment with washed red blood corpuscles and with red corpuscles suspended in citrated saline containing plasma, the latter of which we have already seen have a fragility identical with red corpuscles examined in the form of blood.

The technique employed in obtaining the red cells is in no way altered. Oxygen is bubbled very slowly through a fine capillary tube into a fluid containing the red corpuscles. Frothing in the case of the washed red cells is not troublesome, but may be very inconvenient in the case of the red corpuscles in the citrated saline owing to the albuminous nature of the plasma present in the medium. However, if the stream of oxygen bubbles is kept slow less trouble is encountered.

Take the results from the blood in citrated saline first:

NaCl %.	My own blood in citrated saline.		Blood of healthy female in citrate.		Blood of healthy male in citrate.	
	1 hr. old.	1 hr. old. Oxygen for 30 secs.	1 hr. old.	1 hr. old. Oxygen for 30 secs.	24 hrs. old.	24 hrs. old. Oxygen for 30 secs.
0·350	marked	marked	marked	marked	marked	marked
0·375	distinct	distinct	distinct	distinct	marked	marked
0·400	0	0	0	0	distinct	trace
0·425	0	0	0	0	trace	0
0·450	0	0	0	0	0	0

In the first two examples it is seen that the fragility is practically unaltered and haemolysis has commenced at 0·375 per cent. NaCl solution in the case of the oxygenated red corpuscles as well as in the others, but the haemolysis was of slightly less extent in the latter. In the third case blood was collected and kept for twenty-four hours in an ice safe, one sample being first treated for thirty seconds with oxygen. It will be noticed that the fragility of the oxygenated red corpuscles is less than those not so treated. Now compare the results obtained with washed red corpuscles.

NaCl %.	My own washed red cells.		Washed red corpuscles of healthy female.	
	1 hr. old.	1 hr. old. Oxygen for 30 secs.	1 hr. old.	1 hr. old. Oxygen for 30 secs.
0·350	marked	marked	marked	marked
0·375	marked	marked	marked	marked
0·400	distinct	trace	distinct	trace
0·425	trace	0	0	0
0·450	0	0	0	0

In these results again may be noticed that the red corpuscles which have been oxygenated are slightly less fragile than those over which oxygen has not been passed. It must be remembered that in obtaining the blood precautions are taken that the red corpuscles are well oxygenated, so that, even though one sample of red corpuscles in the above experiment is supposed to be unoxygenated, it does not follow that they are absolutely free from oxygen. Results of experiments will shortly be given which will show more obvious effects of oxygen on the fragility. Meanwhile, I think it may be stated that apparently oxygen does decrease the fragility of the red blood corpuscles to a slight extent.

7. *Effect of carbon dioxide on corpuscular fragility.* Experiments were performed in a similar manner to the preceding, except that carbon dioxide was substituted for oxygen. The carbon dioxide gas similarly was bubbled through a capillary tube for certain specified times.

Blood of healthy male in citrated saline.

NaCl %.	Untreated.	CO_2 20 secs.	Similar corpuscles to the last, but oxygen then passed for 60 secs.
0·350	marked	complete	complete
0·375	marked	complete	marked
0·400	distinct	complete	marked
0·425	trace	complete	distinct
0·450	0	marked	trace
0·475	0	marked	0

All the above examined after 24 hours in ice safe.

	My own blood in citrated saline.		Blood of healthy female in citrated saline.	
NaCl %.	1 hr. old.	CO_2 30 secs.	1 hr. old.	CO_2 30 secs.
0·350	marked	complete	marked	complete
0·375	distinct	marked	distinct	marked
0·400	trace	marked	0	marked
0·425	0	marked	0	marked
0·450	0	marked	0	marked
0·475	0	trace	0	trace

My own blood in citrated saline.

NaCl %.	1 hr. old.	CO_2 20 secs.	Similar corpuscles to the last and then oxygen 60 secs.
0·350	marked	marked	marked
0·375	distinct	marked	marked
0·400	trace	marked	marked
0·425	0	marked	distinct
0·450	0	distinct	0
0·475	0	trace	0

Most interesting results are obtained in these experiments. In all cases the presence of carbon dioxide has increased the fragility of the red corpuscles considerably, or, in other words, the resistance is greatly decreased. Whereas the normal resistance is equivalent to a solution of 0·4 per cent. sodium chloride, the resistance of the red corpuscles which have been carbonated is equivalent to a solution of 0·475 per cent. NaCl or even higher, according to the exposure to carbon dioxide.

That this increased fragility or lessened resistance to weak saline solutions is not due to any acid formation from the carbon dioxide I think may be at once proved by the results of the passage of oxygen over these carbonated red corpuscles. In the preceding table I have given two series of results obtained from such an experiment. In one case it will be observed that 'marked' haemolysis of carbonated red corpuscles occurred in 0·475 per cent. NaCl, and in another case a 'trace' of haemolysis was observed in a similar strength of sodium chloride solution. After oxygen had been passed over these red corpuscles haemolysis was noticed to be only a 'trace' in solutions of 0·45 per cent. and 0·425 per cent. respectively.

Some tabulated results of similar experiments performed on washed red corpuscles may now be given:

	My own washed red corpuscles.		On another occasion.	
NaCl %.	1 hr.	CO_2 30 secs.	CO_2 20 secs.	Similar corpuscles to the last. Oxygen 60 secs.
0·350	marked	complete	complete	marked
0·375	marked	complete	marked	distinct
0·400	distinct	marked	marked	distinct
0·425	trace	marked	marked	trace
0·450	0	marked	distinct	0
0·475	0	marked	trace	0

Similar results are thus obtained again.

The following conclusions are then justified: 1. That the fragility of the red corpuscle is intimately related to its oxygen and carbon dioxide content. 2. That carbon dioxide greatly increases the fragility of the red corpuscle and oxygen decreases the fragility. 3. That the fragility of the red blood corpuscle may be altered from high to low artificially without other apparent injury to the cell.

These results almost make it impossible to emphasize too strongly the importance of using well aerated blood when experimenting on haemolysis, and especially where the possibility of solutions of weak tonicity is present. It would be intensely interesting and important to study the effect of carbon dioxide on the red corpuscle when using a specific haemolysin, but it has been outside the sphere of this investigation.

An interesting observation may be noted here, for the effect of carbon dioxide may give an explanation. To obtain normal serum, blood is allowed to run from a puncture in the thumb into a glass capsule and then centrifugalized after standing half an hour. The serum thus obtained is sometimes found to be haemoglobin stained, and this result may be frequently observed if precautions are not taken to ensure an aerated condition of the blood. Possibly the haemolysis that has occurred here in normal serum can be explained by the increased fragility of the carbonated red corpuscles towards injury by centrifugalizing, or possibly even to saline solution isotonic with serum.

B. *The Fragility of the Red Corpuscles in certain Pathological States.*

1. *Jaundice.* I begin with this pathological condition, for there has been considerable research into the corpuscular fragility in these states, and because remarkable results also have been obtained.

Two definite groups are at once separated by the fragility of the red corpuscles, and they will be investigated under the headings (*a*) Obstructive jaundice, (*b*) Congenital family cholaemia.

(*a*) *Obstructive jaundice.* Limbeck appears to have been the first to describe the corpuscular fragility in these cases, and he gives the figure 0·32 per cent. sodium chloride solution as the strength of saline in which haemolysis starts, noting at the same time that the red corpuscle fragility is constantly decreased in these jaundiced states. Chauffard investigated this subject more fully, and says 0·38 per cent. and 0·28 per cent. sodium chloride solutions cause commencing and complete haemolysis for the red corpuscles examined in the form of blood. Peyton Rous says the two extremes of haemolysis are obtained in 0·46 per cent. and 0·26 per cent. sodium chloride solution respectively when the washed red corpuscles are examined. Vaquez and Ribierre say haemolysis only commences at 0·24 per cent. NaCl. Chalier has compared the fragility of the red corpuscle in blood and of the washed red cell, and gives figures varying between 0·36 per cent. and 0·42 per cent. sodium chloride for commencing haemolysis. Le Gendre and Brulé have similarly compared blood and washed red corpuscles in jaundiced conditions, and give 0·56 per cent. as the strength of sodium chloride solution which just causes haemolysis of blood and washed red corpuscles respectively. With but few exceptions these results show an invariable decrease in fragility of the red corpuscle in obstructive jaundice.

My own results are now given and they emphasize the above observations:

	(1)	(2)		(3)	
NaCl %.	B.	B.	W. R. C.	B.	W. R. C.
0·300	complete	distinct	marked	marked	marked
0·325	marked	trace	marked	marked	marked
0·350	trace	0	distinct	distinct	distinct
0·375	0	0	0	0	distinct
0·400	0	0	0	0	0
0·425	0	0	0	0	0

	(4)		(5)		(6)
NaCl %.	B.	W. R. C.	B.	W. R. C.	B.
0·300	marked	—	marked	—	complete
0·325	marked	marked	distinct	marked	marked
0·350	distinct	marked	trace	marked	marked
0·375	0	distinct	0	distinct	distinct
0·400	0	trace	0	0	0
0·425	0	0	0	0	0

B. = Red corpuscles examined as blood. W. R. C. = Washed red corpuscles.

(1) Deep jaundice: gall-stones. Female, aged 35.
(2) Deep jaundice: carcinoma of pancreas at autopsy. Female, aged 42.
(3) Deep jaundice: ? pancreatitis. Male, aged 66.
(4) Deep jaundice: pancreatitis: ? syphilitic. Female, aged 42.
(5) Deep jaundice: secondary carcinoma of liver. Female, aged 65.
(6) Very faint jaundice: cirrhosis of liver. Female, aged 46.

	(7)		(8)
NaCl %.	B.	W. R. C.	B.
0·300	marked	—	distinct
0·325	marked	—	trace
0·350	marked	marked	0
0·375	trace	marked	0
0·400	0	marked	0
0·425	0	trace	0
0·450	0	0	0

B. = Red corpuscles examined as blood. W. R. C. = Washed red corpuscles.

(7) Faint jaundice: cirrhosis of liver. Male, aged 43.
(8) Deep jaundice: ?gall-stones. Male, aged 46.

If these results are examined it will be found that in the deeply jaundiced cases (1, 2, 3, 4, 5, and 8) the red corpuscle fragility is markedly decreased. In no case does haemolysis of the blood occur until a dilution of 0·35 per cent. sodium chloride is tried, and in two of the cases there is only a 'trace' of haemolysis in 0·325 per cent. saline. When this is compared with the washed red corpuscles of the same cases it is again found that the fragility is decreased; in one case haemolysis commences in 0·400 per cent. NaCl, in two cases this commences at 0·375 per cent. NaCl, and in one other case there is only faint haemolysis in 0·350 per cent. NaCl.

It appears then that the decreased fragility of the red corpuscles in cases of jaundice is shown not only when the red cells are examined as blood but also when the red corpuscles are washed free from plasma. The decreased fragility can be put down to the jaundiced state, for in my own series at least four or five different diseases are represented.

The faintly jaundiced cases (6 and 7) show no apparent decrease in the corpuscular fragility. Both were cases of alcoholic cirrhosis of the liver, and the fragility, whether examined in the form of blood or washed red corpuscles, appears to be normal.

It is usually assumed that hypotonic haemolysis merely is an indication of the salt concentration within the red corpuscle envelope, and that variations in tonicity alone may increase or diminish to a high degree the corpuscular fragility to hypotonic haemolysis. McNeil has lately explained the decreased fragility of the red corpuscles in jaundice as due to the increased tonicity of the blood in this condition. It is true the decreased fragility to hypotonic solutions of the red corpuscles examined as blood may be explained in this way, but the decreased fragility persists after washing the red corpuscles and keeping them in 0·85 per cent. sodium chloride, which is usually considered to be isotonic with normal blood. Surely after being kept in 0·85 per cent. sodium chloride solution they ought to correspond in fragility to normal washed red corpuscles if their original decreased fragility was merely due to increased salt concentration of the plasma.

(*b*) *Congenital family cholaemia.* Turning now to the group represented by the above title we find a very different state of affairs. Chauffard apparently

was the first to recognize the extraordinary corpuscular fragility in these cases. He gives the figures for two cases, haemolysis commencing in 0·68 per cent. and 0·52 per cent. sodium chloride solution respectively, complete haemolysis being obtained in 0·34 per cent. and 0·18 per cent. NaCl solutions. Peyton Rous has examined the fragility, using washed red corpuscles in a 1 in 3 dilution, and states that haemolysis starts in 0·75 per cent. NaCl solution and is complete in 0·55 per cent. saline, adding further the interesting statement that the fragility of these red corpuscles towards a specific haemolysin is normal. Tileston and Griffin also examining the washed red corpuscles find that haemolysis begins in 0·7 per cent. saline in these congenital cases. Chalier gives the figures 0·66 per cent. to 0·6 per cent. NaCl in one case and 0·56 per cent. NaCl in another. Le Gendre and Brulé have described two cases of congenital haemolytic jaundice, and state that haemolysis towards salt solution commences in 0·62 per cent. NaCl for the red corpuscles in blood and at 0·72 per cent. NaCl for the washed red corpuscles. Cade examined the blood in a family of haemolytic individuals and found a minimal resistance for the washed red corpuscles of 0·42 per cent., 0·60 per cent., 0·58 per cent., and 0·56 per cent. NaCl respectively for the father and three children of the family. Hawkins and Dudgeon find haemolysis commences on the addition of blood to 0·6 per cent. NaCl solution in proportion of 1 in 11. Hutchison and Panton find haemolysis commences in their two cases at 0·6 per cent. and 0·5 per cent. salt solution respectively.

There is much evidence, then, that in congenital family cholaemia the red cells are defective in some way. In my own series additional evidence is found to support this view, and in the table given the red corpuscles are examined as blood and as washed red corpuscles.

	(1)		(2)	
NaCl %.	B.	W.R.C.	B.	W.R.C.
0·575	marked	marked	marked	marked
0·600	marked	marked	trace	marked
0·625	trace	marked	trace	distinct
0·650	0	trace	0	trace
0·675	0	0	0	0

	(3)		(4)	
NaCl %.	B.	W.R.C.	B.	W.R.C.
0·400	complete	—	—	—
0·500	marked	—	—	—
0·525	marked	—	—	—
0·550	marked	—	—	—
0·575	marked	marked	marked	marked
0·600	marked	marked	marked	marked
0·625	trace	distinct	trace	marked
0·650	0	trace	0	distinct
0·675	0	0	0	trace
0·700	0	0	0	0

(1) Male, aged 12. (2) Female, aged 14. (3) Female, aged 30.
(4) Male, aged 53—father of the former three cases.

	(5)		(6)			
	W. R. C.	W. R. C.	B.	W. R. C.	W. R. C.	W. R. C.
NaCl %.		O_2 60 secs.			O_2 60 secs.	CO_2 10 secs.
0·500	marked	marked	marked	marked	distinct	marked
0·525	marked	marked	marked	marked	distinct	marked
0·550	distinct	distinct	distinct	distinct	trace	marked
0·575	distinct	distinct	trace	distinct	trace	distinct
0·600	distinct	trace	0	distinct	trace	distinct
0·625	distinct	trace	0	trace	trace	distinct
0·650	trace	0	0	0	0	trace
0·675	0	0	0	0	0	trace
0·700	0	0	0	0	0	0

(5) Female, aged 44—mother of the following case. (6) Female, aged 11.

Two families are represented in the above series. In four cases the red corpuscle resistance examined as blood has been found to break down in 0·625 per cent. sodium chloride solution, in one case this has occurred at 0·575 per cent. NaCl. As regards the washed red corpuscles, haemolysis just commences in 0·65 per cent. NaCl in four cases, in 0·625 per cent. NaCl in one case, and 0·675 per cent. NaCl in another case. The fragility is slightly increased as a result of washing the corpuscles in all cases and to the same extent as occurs in normal blood, that is, the washed red corpuscles have a decreased resistance compared with blood to the extent of 0·025 per cent. to 0·05 per cent. of sodium chloride.

In recording my investigations on normal blood it will be remembered that interesting results were obtained from the effect of oxygen and carbon dioxide on the red corpuscle fragility. It at once becomes necessary to examine whether the extraordinary increased fragility of the red corpuscles in this disease might be decreased by the action of oxygen. In the above table (cases 5 and 6) two such experiments are recorded, oxygen being allowed to bubble slowly over the washed red corpuscles; the effect of passing carbon dioxide for ten seconds over the red corpuscles being also investigated. The fragility of the washed red corpuscles in this disease is certainly slightly decreased by oxygen, and to about the same extent that the normal red corpuscle fragility can be decreased by oxygen, but still the fragility is very marked. Again, as regards the effect of carbon dioxide, the fragility is increased just as was noted for the normal red corpuscle.

The red corpuscles in congenital family cholaemia appear to be extraordinarily fragile towards hypotonic solutions, and this fragility is in no way connected with the fragility imparted to the red corpuscle by carbon dioxide, but appears rather to be due to a defective structure of the red corpuscle.

2. *The corpuscular fragility in acute infective conditions.* (*a*) *Pyaemia and septicaemia.* There appear to be but scanty observations in these conditions, so that I proceed to give my own results at once:

	(1)	(2)	(3)	(4)		(5)	
NaCl %.	B.	B.	B.	B.	W. R. C.	B.	W. R. C.
0·300	marked	marked	complete	marked	complete	marked	marked
0·325	marked	marked	marked	marked	marked	marked	marked
0·350	0	trace	marked	marked	marked	trace	marked
0·375	0	0	trace	marked	marked	0	trace
0·400	0	0	0	trace	trace	0	0
0·425	0	0	0	0	trace	0	0
0·450	0	0	0	0	0	0	0

	(6)	
NaCl %.	B.	W. R. C.
0·300	marked	marked
0·325	marked	marked
0·350	trace	trace
0·375	0	0
0·400	0	0
0·425	0	0

B. = Blood. W. R. C. = Washed red corpuscles.

(1) Puerperal septicaemia: streptococcal infection. Thirtieth day of illness. Female, aged 26, not fatal.
(2) Streptococcal arthritis. Fifth day of illness. Female, aged 26, not fatal.
(3) Hernia: streptococcal infection of wound. Third day of illness. Female, aged 19, not fatal.
(4) Puerperal septicaemia: streptococcal infection. Eighteenth day of illness. Female, aged 36, not fatal (mild case).
(5) Puerperal septicaemia. Examined on tenth and sixteenth days of illness. Female, aged 20, not fatal.
(6) Pyaemia. Examined on tenth and eleventh days of illness. Male, aged 38. Fatal on twelfth day.

It would be expected that in such acute infective conditions as pyaemia and septicaemia an increased fragility of the red corpuscles would be found. Quite the contrary results have been obtained, as will be seen by the above tables. In all cases, except (3) and (4), the fragility towards weak salt solutions has been decreased, haemolysis not commencing until 0·35 per cent. NaCl is reached in the case of blood itself, while for the washed red corpuscles haemolysis commences in 0·35 per cent. to 0·375 per cent. NaCl. In the two exceptions, the first was examined on the third day of illness and the second was very mild in character, which may be the reason for their close approximation to the normal type. In all other cases the patients were extremely ill with high fever and obvious toxaemia.

It may be considered, then, that in pyaemia and septicaemia the fragility of the red corpuscles is slightly decreased.

Sacquépee has recorded an interesting case of streptococcal infection of the thigh which was accompanied by jaundice, and he found that the minimal resistance of the washed red corpuscles was obtained in 0·52 per cent. NaCl, and that this resistance slowly increased to 0·50 per cent. NaCl, and then decreased again with improvement in the leg condition. Knowing the effect of jaundice on the red cell resistance I think it doubtful whether this result can be properly included under the heading of septicaemia.

(*b*) *Erysipelas and cellulitis.* Limbeck states that in cases of erysipelas the

resistance to distilled water is diminished. Dudgeon has recorded a case of erysipelas in which the fragility of the red corpuscles was much increased. I have been unfortunate in not obtaining cases of this condition, and I can only record one mild case of erysipelas affecting the legs. In this case haemolysis of the blood commenced at 0·4 per cent. NaCl and was complete at 0·3 per cent. NaCl, which approximates almost exactly with the normal condition.

I have examined the fragility of the red corpuscles as blood in only one case of cellulitis and it proved to be within the normal limits.

(*c*) *Scarlet fever.* The facilities for investigating the fragility in this disease have not been great. I have had no opportunity of examining the blood as such, but the blood has been collected into citrated saline, and in this condition the red corpuscles have been examined. It will be remembered that the fragility of the corpuscles in this condition corresponds to the fragility of the red corpuscles in normal blood.

	(1)		(2)		(3)	
NaCl %.	R. C.	W. R. C.	R. C.	W. R. C.	R. C.	W. R. C.
0·325	marked	marked	marked	marked	marked	marked
0·350	marked	marked	marked	distinct	distinct	trace
0·375	distinct	marked	trace	trace	trace	trace
0·400	trace	distinct	0	0	0	0
0·425	0	trace	0	0	0	0
0·450	0	0	0	0	0	0

	(4)		(5)	
NaCl %.	R. C.	W. R. C.	R. C.	W. R. C.
0·325	marked	marked	marked	marked
0·350	marked	marked	marked	distinct
0·375	marked	distinct	distinct	distinct
0·400	marked	trace	trace	trace
0·425	trace	trace	trace	trace
0·450	0	0	0	0

R. C. = Red corpuscles in citrated plasma. W. R. C. = Washed red corpuscles.

(1) Aged 6. Thirteenth day: no complications.
(2) Aged 20. Seventh day: no complications.
(3) Aged 8. Eighth day: no complications.
(4) Aged 16. Fifteenth day: nephritis present.
(5) Aged 27. Fifteenth day: no complications.

Two cases at the seventh and eighth days respectively show less fragility than the other cases which were examined later in the disease. In all but one case an interesting result is shown in that the fragility of the washed red corpuscle does not differ from that of the red corpuscles examined in citrated plasma. Such a result is rarely observed in normal or any other abnormal state. Except for this difference the results show but little variation from the normal limits.

Teissier and Benard state that the fragility of red corpuscles in cases of scarlet fever is normal unless jaundice is present as a complication, when the fragility is increased, but this condition must be very rare.

(*d*) *Pneumonia.* Limbeck states that the fragility of the red corpuscles in this disease is increased. My own results scarcely confirm this.

NaCl %.	(1) B.	(2) B.	(3) B.	(4) B.	(4) W.R.C.
0·300	complete	complete	complete	trace	marked
0·325	complete	complete	marked	trace	distinct
0·350	marked	marked	marked	0	trace
0·375	0	marked	trace	0	0
0·400	0	0	0	0	0

NaCl %.	(5) B.	(5) W.R.C.	(6) B.	(6) W.R.C.	(7) B.	(7) W.R.C.
0·300	complete	complete	complete	complete	complete	complete
0·325	marked	marked	marked	marked	marked	marked
0·350	distinct	marked	distinct	marked	distinct	marked
0·375	0	trace	trace	marked	trace	distinct
0·400	0	0	0	trace	0	trace
0·425	0	0	0	0	0	0

NaCl %.	(8) B.	(8) W.R.C.	(9) B.	(9) W.R.C.
0·300	marked	complete	marked	complete
0·325	marked	marked	marked	marked
0·350	trace	distinct	trace	marked
0·375	0	trace	0	trace
0·400	0	0	0	0

B. = Red corpuscles examined as blood. W.R.C. = Washed red corpuscles.

(1) Male, aged 15. Sixth day of illness. Temp. 103. Crisis on seventh day.
(2) Male, aged 29. Fourth day of illness. Temp. 102. Crisis on fourth day.
(3) Male, aged 19. Sixth day of illness. Temp. 101. Crisis on sixth day.
(4) Male, aged 42. Sixth day of illness. Temp. 102. Lysis.
(5) Male, aged 32. Third day of illness. Temp. 102. Lysis.
(6) Male, aged 45. Fifth day of illness. Temp. 100. Lysis.
(7) Male, aged 55. Tenth day of illness. Temp. 101. Lysis.
(8) Male, aged 10. Third day of illness. Temp. 104. Crisis fifth day.
(9) Male, aged 15. Fifth day of illness. Temp. 103. Crisis sixth day.

These results show a uniform decrease in fragility of the red corpuscles, whether examined in the form of blood or in the washed state. Minimal resistance in the case of the red corpuscles examined in the form of blood is represented by sodium chloride solution of 0·35 per cent. to 0·375 per cent., and even with the washed red corpuscles haemolysis is not noticed in most of the cases until 0·375 per cent. NaCl solution is reached.

This conclusion may then be stated, that there is a slight decrease in the fragility of the red corpuscles in pneumonia. There does not appear to be any noticeable difference in the fragility of those cases that tend to improve rapidly and those cases that become complicated in some way.

(*e*) *Acute rheumatism.* There does not appear to be anything of note in the fragility of the red corpuscles in this disease beyond the fact that this approximates the normal condition, but with a tendency to be a trifle more resistant. Similarly, the washed red corpuscles behave like normal washed red corpuscles towards hypotonic solutions. I have been unable to compare these results with those of other observers, for none appear to have been recorded.

Reviewing the fragility of the red corpuscles in acute infective conditions but little change from the normal is found, except in pneumonia and pyaemia, where there is evidence that the corpuscular fragility is somewhat decreased.

From the nature of the illnesses it would be expected more positive results would have been obtained.

3. *The red corpuscle fragility in certain chronic diseases.* (*a*) *Chronic sepsis.* Three cases of empyema with sinuses of long duration were examined; both showed commencing haemolysis in 0·375 sodium chloride and complete haemolysis in 0·3 NaCl, which results may be considered normal.

(*b*) *Tuberculosis.* Cases of pulmonary tuberculosis, tuberculous pleurisy, and tuberculous peritonitis were investigated; the red corpuscle fragility alone being examined in the form of blood. The only conclusion obtained was that the fragility of the red corpuscles does not differ from normal, but in the three cases examined the maximal resistance was apparently increased slightly. Landouzy has recorded a case of pulmonary tuberculosis that gave interesting results as regards the fragility, but unfortunately the case was complicated with jaundice, and for this reason ought not to be included under this heading. He states that the haemolysis commenced in 0·54 per cent. sodium chloride, and that the fragility decreased with the improvement in the lung condition.

(*c*) *Malignant disease.* I have only examined one case that has been unassociated with jaundice. This was a case of carcinoma of the stomach, and the fragility of the red corpuscles as blood did not differ from the normal condition.

Lang has investigated this side of the subject rather fully and finds the fragility usually decreased. Haemolysis for cases of carcinoma of stomach he finds commences in 0·32 per cent. sodium chloride. This shows a good deal less fragility than Chalier finds even though his cases were associated with jaundice. The latter observer gives 0·36 per cent. NaCl for the minimal resistance.

(*d*) *Graves's disease.* No previous observations on the red cell fragility appear to have been made.

	(1)	(2)	(3)	(4)	(5)
NaCl %.	B.	B.	B.	B.	B.
0·300	complete	complete	marked	complete	complete
0·325	marked	marked	marked	marked	complete
0·350	distinct	trace	trace	trace	marked
0·375	trace	trace	trace	trace	trace
0·400	0	0	0	0	0

	(6)	(7)	(8)		(9)	
NaCl %.	W. R. C.	W. R. C.	B.	W. R. C.	B.	W. R. C.
0·300	complete	complete	complete	complete	marked	marked
0·325	complete	complete	marked	complete	distinct	marked
0·350	marked	marked	marked	marked	trace	distinct
0·375	marked	marked	trace	marked	0	trace
0·400	distinct	marked	0	trace	0	0
0·425	distinct	distinct	0	0	0	0
0·450	trace	trace	0	0	0	0

(1) Female, aged 18. Symptoms four months.
(2) Female, aged 26. Symptoms three months.
(3) Female, aged 31. Symptoms twelfth months.
(4) Female, aged 25. Symptoms seven years. (5) Female, aged 23.
(6) Female, aged 18. (7) Female, aged 26. Symptoms three years.
(8) Female, aged 32. Treated with doses of NaCl.
(9) Female, aged 23. Treated with doses of NaCl.

All the above cases with two exceptions (8 and 9) appear to have about the normal fragility for the red corpuscles. In two cases (8 and 9) interesting results are shown; the fragility in these cases appears to be lowered. Especially is this so with the washed red corpuscles. Whereas the normal minimal resistance of washed red cells in this disease is about 0·45 per cent. NaCl, the two exceptions above quoted show a minimal resistance in 0·4 per cent. and 0·375 per cent. sodium chloride solution. Interest is attached to these results because the two patients in question had been treated with fairly large doses of sodium chloride. Whether this can be considered to be cause and effect is difficult to decide owing to the scanty evidence, but there is confirmation in the records of other observers that drugs can alter the fragility of the red corpuscle.

Sutherland and McCay state that there is an increased resistance (as determined by haemolysis with distilled water) caused by the ingestion and absorption of chlorides in the case of rabbits' blood. Gunn has obtained similar results by the action of arsenious acid on human red corpuscles.

(*e*) *Nephritis.* The cases examined have been almost solely cases of tubal nephritis, one case of interstitial nephritis is included. Great expectations were entertained that results widely differing from normal would be obtained, and with this hope patients with marked oedema were chosen for examination, knowing that diminished salt secretion is associated with these states.

	(1)	(2)	(3)	(4)	(5)	(6)
NaCl %.	B.	B.	B.	B.	B.	B.
0·300	complete	complete	complete	complete	complete	complete
0·325	marked	marked	marked	marked	complete	marked
0·350	trace	trace	trace	marked	marked	trace
0·375	0	0	0	trace	distinct	0
0·400	0	0	0	0	0	0

	(7)	(8)	(9)		(10)	
NaCl %.	B.	B.	B.	W. C. R.	B.	W. R. C.
0·300	complete	complete	complete	complete	complete	complete
0·325	marked	marked	marked	marked	marked	complete
0·350	marked	marked	distinct	marked	marked	marked
0·375	trace	trace	0	distinct	trace	marked
0·400	0	0	0	trace	0	marked
0·425	0	0	0	0	0	trace
0·450	0	0	0	0	0	0

	(11)	
NaCl %.	B.	W. R. C.
0·300	complete	complete
0·325	marked	complete
0·350	marked	marked
0·375	distinct	marked
0·400	0	marked
0·425	0	trace
0·450	0	0

(1) Male, aged 19. (2) Male, aged 29. Uraemia. Fatal.
(3) Male, aged 29. Fatal. (4) and (5) Female, aged 9. Oedema marked.
(6) Female, aged 25. (7) Male, aged 19. Oedema.
(8) Male, aged 52. Interstitial nephritis. Blood pressure 200 mm. Hg.
(9) Male, aged 12. Oedema. (10) Male, aged 32. Marked oedema.
(11) Male, aged 25. Marked oedema.

On examining these results, and other results have been obtained similar to these, it appears that the minimal resistance of the red corpuscles examined in the form of blood is never obtained until a 0·35 per cent. or 0·375 per cent. of sodium chloride is reached. In the case of the washed red corpuscles the first sign of haemolysis is usually obtained in 0·4 per cent. to 0·425 per cent. solution of sodium chloride.

It may be concluded, then, that probably there is a slight decrease in the fragility of the red corpuscles in chronic nephritis. It is difficult to assert that this result is due to the increased salt concentration of the blood, but significance may be attached to the results when we compare them with the results obtained by treating cases of Graves's disease with salt and at the same time knowing that in tubal nephritis patients associated with oedema there is a diminished salt secretion.

(*f*) *Diabetes.* The results of experiments with diabetes cases will now be given.

	(1)	(2)	(3)	(4)	
NaCl%.	B.	B.	B.	B.	W. R. C.
0·300	marked	complete	complete	complete	complete
0·325	marked	marked	complete	marked	complete
0·350	distinct	marked	marked	marked	marked
0·375	trace	distinct	distinct	marked	marked
0·400	0	trace	trace	distinct	marked
0·425	0	0	0	—	distinct
0·450	0	0	0	—	trace

	(5)		(6)		(7)	
NaCl%.	B.	W. R. C.	B.	W. R. C.	B.	W. R. C.
0·300	complete	complete	complete	complete	marked	complete
0·325	complete	complete	complete	complete	marked	marked
0·350	marked	marked	marked	marked	distinct	marked
0·375	marked	marked	marked	marked	trace	distinct
0·400	trace	marked	trace	marked	0	0
0·425	0	trace	0	trace	0	0
0·450	0	0	0	0	0	0

	(8)		(9 a)		(9 b)	
NaCl%.	B.	W. R. C.	B.	W. R. C.	B.	W. R. C.
0·300	marked	complete	complete	complete	complete	complete
0·325	marked	marked	complete	marked	complete	complete
0·350	distinct	marked	marked	marked	complete	complete
0·375	trace	distinct	marked	marked	marked	marked
0·400	0	0	distinct	trace	marked	marked
0·425	0	0	—	0	marked	marked
0·450	0	0	—	0	distinct	distinct
0·475	0	0	—	0	trace	trace
			Date 16/2/10.		Date 24/2/10.	

(1) Female, aged 29. History eighteen months. Sugar 4,800 grains daily. Acetone and diacetic acid. Fatal.
(2) Male, aged 43. History four months. Sugar 3,000 grains daily. No acetone or diacetic.
(3) Female, aged 40. History. No acetone or diacetic.
(4) Female, aged 68. Very little sugar.
(5) Male, aged 18. History four months. Sugar 1,800 grains daily. No acetone or diacetic.
(6) Male, aged 41. History six years. Sugar 100 grains daily. Diacetic and acetone present.
(7) Male, aged 37. Sugar 1,500 grains. No acetone or diacetic.
(8) Female, aged 53. History three months. Sugar 2,500 grains daily. Acetone and diacetic present. Fatal.
(9 a) Male, aged 55. History three months. Sugar 1,500 grains daily. Acetone and diacetic present.
(9 b) Male, aged 55. Sugar 2,500 grains. Acetone and diacetic present.

	(9 c)		(9 d)	
NaCl %.	B.	W. R. C.	B.	W. R. C.
0·300	complete	complete	complete	complete
0·325	complete	complete	complete	complete
0·350	marked	marked	complete	complete
0·375	distinct	distinct	marked	marked
0·400	distinct	trace	marked	distinct.
0·425	0	0	distinct	0
0·450	0	0	0	0
	Date 3/3/10.		Date 21/3/10.	

(9 c) Male, aged 55. Sugar 1,200 grains. No acetone or diacetic.
(9 d) Male, aged 55.

The results obtained, owing to their variable nature, give but little opportunity to formulate a conclusion. The first six cases show results that may be considered to be normal. Cases 7 and 9 inclusive have given rather varying results, but in one particular they all agree in showing that the fragility of the washed red corpuscles and of the corpuscles examined as blood does not differ, and further, if there is any slight difference it usually is that the fragility of the washed red corpuscles is less than that of the blood. These are among the few examples occurring in the course of the whole investigation where the fragility of the red corpuscles remains unaltered after being washed in normal saline. In the last case, examined on four different occasions, this same result was obtained, but at the same time there is noticed a considerable variation in the fragility of the red corpuscles from day to day, on one occasion the minimal resistance being found in 0·475 per cent. sodium chloride solution. The sugar outputs on the days in question were different, but I do not think this explanation is worthy of consideration; it is more probable that some obscure relation between the alkalinity of the blood and the carbon dioxide tension is the explanation, for we know that in diabetes there is considerable variation in the alkalinity of the blood dependent on the extent to which the alkalis of the blood are fixed by the acids found in diabetic conditions.

(*g*) *Syphilis.* A few cases only have been examined and in only one case have the washed red blood corpuscles been used.

	(1)	(2)	(3)	(4)	(5)
NaCl %.	B.	B.	B.	B.	W. R. C.
0·300	marked	complete	complete	marked	complete
0·325	marked	marked	marked	marked	complete
0·350	marked	marked	marked	marked	marked
0·375	trace	distinct	trace	trace	marked
0·400	0	0	0	0	marked
0·425	0	0	0	0	distinct
0·450	0	0	0	0	0

(1) Male, aged 35. Tertiary stage.
(2) Female, aged 30. Secondary stage.
(3) Male, aged 27. Secondary stage.
(4) Male, aged 31. Gummatous meningitis.
(5) Male, aged 20. Secondary stage.

Slight decreased fragility is shown in all cases in that minimal resistance is not observed until a solution of sodium chloride of 0·375 per cent. strength is

used: but as normal resistance varies between 0·375 per cent. and 0·4 per cent. NaCl solution not much emphasis can be laid on the change in syphilitic conditions.

Chalier states that he finds commencing haemolysis in 0·42 per cent. NaCl and complete haemolysis in 0·25 per cent. sodium chloride solution for the washed and unwashed red corpuscles when using a 1 in 70 dilution. These figures agree with mine if we take into consideration the total salt concentration that is present in the tube showing commencing haemolysis where there is 1 volume of blood (assumed to be 0·85 per cent. NaCl in strength) and 9 volumes of 0·375 per cent. NaCl.

(*h*) *General paralysis and tabes dorsalis.* The patients examined have been too few to warrant any definite conclusion in these diseases, but results as far as they go indicate a negligible difference from the normal fragility. Two cases of tabes and one case of general paralysis alone were examined.

4. *The red corpuscle fragility in certain blood diseases.* (*a*) *Chlorosis.* Only one case was examined, but it was severe in type. The fragility did not differ appreciably from the normal state. Limbeck states that his two cases showed commencing haemolysis in 0·38 per cent. to 0·4 per cent. NaCl, with which my figures practically agree.

(*b*) *Pernicious anaemia.*

	(1)	(2)		(3)		(4)
NaCl %.	B.	B.	W. R. C.	B.	W. R. C.	W. R. C.
0·300	complete	complete	complete	marked	complete	complete
0·325	marked	marked	complete	marked	complete	complete
0·350	marked	marked	marked	marked	marked	marked
0·375	trace	trace	marked	trace	marked	marked
0·400	0	0	distinct	0	marked	distinct
0·425	0	0	trace	0	distinct	trace
0·450	0	0	0	0	trace	0
0·475	0	0	0	0	0	0

(1 Male, aged 69. Reds 1 million. Whites 1,000. On arsenic fourteen days.
(2) Female, aged 35. Reds 1½ millions. Whites 3,000. On arsenic three days.
(3) Male, aged 39. Reds 2 millions. Whites 3,750. On quinine only.
(4) Female, aged 40. Reds 4½ millions. Whites 4,000. On atoxyl.

It was hoped that some alteration in the red corpuscle fragility was to be discovered in this disease; there, however, appears to be but a negligible alteration from the normal fragility. The possibility of some alteration in the fragility has, however, not been disproved entirely for these cases if we take into consideration the fact that the patients were being treated with arsenic, for Gunn has shown that an increased resistance of the red corpuscles is obtained under those conditions.

(*c*) *Myelaemia.* I have had the opportunity of examining two cases, but again results show inappreciable differences from the normal fragility. Results are given below, for they appear to be the first on record.

	(1)	(2)	
NaCl %.	B.	B.	W. R. C.
0·300	complete	complete	complete
0·325	marked	marked	marked
0·350	marked	distinct	distinct
0·375	marked	trace	distinct
0·400	trace	0	trace
0·425	0	0	trace
0·450	0	0	0

(1) Male, aged 17. (2) Male, aged 22.

(*d*) *Lymphaemia.* An opportunity occurred to examine the fragility of the red corpuscles in one case; there was extreme anaemia, and death occurred after a short illness. Even in as acute an illness as this there was no apparent alteration in the fragility of the red corpuscles towards weak saline solutions, whether the red corpuscles were examined as blood or after washing.

(*e*) *Purpura.* One case was examined, a boy of eleven who presented the symptoms and signs of Henoch's purpura. It is not justifiable to draw any conclusions from one case, so that I state the result only. Commencing haemolysis was first noticed in 0·375 per cent. and 0·4 per cent. NaCl for the blood and washed red corpuscles respectively: in the latter case there is apparently a slight decreased fragility.

(*f*) *Paroxysmal haemoglobinuria.* The two patients examined gave practically a normal result. In one case there had been no recent attack, in the other an attack had just concluded and the urine was still characteristic.

(*g*) *Haemophilia.* Only one case was available, a boy of thirteen years. Haemolysis was marked at 0·3 per cent. NaCl, and faint at 0·35 per cent NaCl. when the red corpuscles were examined as blood. The patient was not taking calcium salts in any form. The red corpuscles in this case had a slightly decreased fragility which is against the evidence of other observers, Albertoni finding an increased fragility in this condition.

(*h*) *Malaria.* The fragility of the red corpuscles was tested in one case on two occasions just as a rigor had been completed: a normal result was obtained on each occasion. The patient had a single infection with the benign tertian parasite: unfortunately no examination of the fragility of the red corpuscles after recovery from the attack was made.

5. *Cyanosed conditions.* I have not been able to examine cases of congenital heart disease: the investigation given below was conducted on an obese man of 46 with extreme cyanosis. Examinations were made on three consecutive days.

NaCl %.	B.	W. R. C.	B.	W. R. C.	B.	W. R. C.
0·300	complete	complete	complete	complete	complete	complete
0·325	complete	complete	complete	complete	complete	complete
0·350	marked	marked	marked	marked	marked	marked
0·375	marked	marked	marked	marked	marked	marked
0·400	marked	marked	marked	marked	distinct	marked
0·425	distinct	distinct	distinct	distinct	trace	distinct
0·450	trace	trace	trace	trace	0	trace
0·475	0	0	0	0	0	0
Date	27/4/10		28/4/10		29/4/10	

Results of great interest were obtained in this case. An increased fragility of the red corpuscles examined as blood is to be noted, while the fragility of the washed red corpuscles remains normal. Similar results were obtained on each day except the last, when, apparently owing to the improving condition of the patient, the fragility of the unwashed red corpuscles has decreased, the washed red corpuscles still having their original resistance towards hypotonic salt solution.

Conclusions.

Reviewing the investigation as a whole, the results appear somewhat disappointing owing to their negative character: especially in the various pathological conditions positive results were expected.

The fragility of the red corpuscles appears to be extraordinarily constant in normal and pathological conditions.

The following conclusions appear to be justified:

1. The minimum resistance of the normal red blood corpuscle when examined as blood is shown as commencing haemolysis in 0·375 per cent. to 0·4 per cent. sodium chloride solution when a 1 in 10 dilution is used. The resistance of washed red corpuscles is normally less than that of the unwashed corpuscle, the minimal resistance being obtained in a salt solution of 0·425 per cent. to 0·45 per cent. sodium chloride solution.

2. The necessity of employing a constant dilution of blood in recording results in order that they may be comparable has been demonstrated, and the lack of this precaution is the cause of the discordant results of other observers.

3. The rapidity with which washed red corpuscles in normal saline alter their resistance has been shown, and the necessity of experiments being conducted with freshly-washed red corpuscles has been pointed out. Such deterioration is not demonstrable in red corpuscles kept in citrated plasma for 24 to 48 hours.

4. Different anticoagulants may be used, except leech extract, without altering the red corpuscle fragility, provided the red corpuscles are subsequently washed with normal saline solution.

5. Oxygen is capable of decreasing the fragility of the red blood corpuscle. Carbon dioxide has a very marked effect in increasing the fragility, and these two effects are interchangeable.

6. The decreased fragility of the red corpuscles in obstructive jaundiced conditions has been confirmed.

7. The increased fragility of the red corpuscles in congenital acholuric jaundice is confirmed. The effect of oxygen and carbon dioxide on these corpuscles has been shown not to differ from the effect on normal corpuscles.

8. A slightly decreased fragility of the red corpuscles has been demonstrated in pyaemia, septicaemia, pneumonia, and chronic tubal nephritis.

9. An increased fragility is shown in cyanosed states.

10. Fragility appears to be normal in erysipelas, scarlet fever, Graves's disease, carcinoma, syphilis, general paralysis, tabes, chlorosis, pernicious anaemia, myelaemia, lymphaemia, purpura, paroxysmal haemoglobinuria, and malaria.

11. The fragility of the red corpuscles in diabetes appears to vary considerably.

12. The effect of ingestion of sodium chloride has been noticed to decrease the fragility of red corpuscles.

I have pleasure in taking this opportunity of expressing my thanks to Dr. Dudgeon, at whose suggestion this investigation was undertaken, and to the Physicians and Surgeons of St. Thomas's Hospital for the use of the material in their wards.

REFERENCES.

1. Allbutt, *System of Medicine*.
2. Albertoni, quoted by Ewing.
3. Bramachari, *Biochemical Journal*, Liverpool, 1907, 96 ; 1909, iv. 59, 280; 1911, v. 291.
4. Buckmaster, *Morph. of Normal and Path. Blood*, Lond., 1906.
5. Cade, *Bull. et Mém. Soc. méd. d. hôp. de Paris*, 1908, 3e sér., xxv. 421.
6. Chalier, *Presse médicale*, Paris, 1910, xviii. 454.
7. Chauffard, *Semaine médicale*, Paris, 1907, 25; 1908, 49.
8. Chauffard et Rendu, *Presse médicale*, Paris, 1907, xv. 345.
9. Chauffard et Troisier, *Bull. et Mém. Soc. méd. d. hôp. de Paris*, 1909, 3e sér., xxvi. 7.
10. Christophers and Bentley, *Scientific Memoirs Govt. India*, 1908, N. S., no. 35, pp. 76, 117, 130.
11. Delille, *Semaine médicale*, Paris, 1909, 83.
12. Dudgeon, *Proc. Roy. Soc.*, Ser. B, 1909, lxxxi. 207.
13. Ewing, *Clinical Pathology of the Blood*, Lond.
14. Feuillié, *Compt. rend. Soc. de Biol.*, Paris, 1908, lxv. 626, 686.
15. Gay, *Journ. Med. Research*, Boston, 1905, xvii. 321.
16. Le Gendre et Brulé, *Bull. et Mém. Soc. méd. d. hôp. de Paris*, 1909, 3e sér., xxvi. 112.
17. Gunn, *Brit. Med. Journal*, 1908, ii. 145.
18. Hamburger, *Centralbl. für Physiol.*, 1894, viii. 365.
19. Hamburger, *Arch. f. path. Anat. u. Physiol.*, Berlin, 1895, cxl. 503.
20. Hamburger, *Journ. de Physiol. norm. et path.*, Paris, 1909, xi. 301.
21. Hawkins and Dudgeon, *Quart. Journ. Med.*, Oxford, 1908–9, ii. 172.
22. Höber, *Biochem. Zeitschr.*, Berlin, 1908, xiv. 209.
23. Hutchison and Panton, *Quart. Journ. Med.*, Oxford, 1908–9, ii. 432.
24. Iscovesco et Salignat, *Compt. rend. Soc. de Biol.*, 1907, lxiii. 778.
25. Landouzy, *Presse médicale*, Oct. 10, 1910.
26. Lang, *Zeitschr. für klin. Med.*, Berlin, 1902, xlvii. 153.
27. Limbeck, *Pathology of the Blood*, Lond., 1901 (New Syd. Soc.).
28. McCay, *Biochemical Journal*, Liverpool, 1908, iii. 97.
29. McNeil, *Journ. of Path. and Bacteriol.*, Camb., 1911, xv. 70.
30. Parkes Weber, *Amer. Journ. Med. Sci.*, 1909, N. S., cxxxviii. 24. *International Clinics*, 1909, vol. ii.

31. Parkes Weber and Dorner, *Lancet*, Lond., 1910, i. 227.
32. Peyton Rous, *Journ. Exper. Med.*, New York, 1909, xi. 763.
33. Ribierre, *Thèse de Paris*, 1903.
34. Sacquépee, *Bull. et Mém. Soc. méd. des hôp. de Paris*, 1908, 3e sér., xxv. 361; 1909, xxvi. 164.
35. Smith, *Journ. Med. Research*, Boston, 1904, xvi. 385.
36. Sutherland and McCay, *Biochemical Journal*, Liverpool, 1911, v. 1.
37. Teissier et Benard, *Presse médicale*, 1910.
38. Tileston and Griffin, *Amer. Journ. Med. Sci.*, 1910, N. S., cxxxix. 847.
39. Vaquez et Ribierre, *Compt. rend. Soc. de Biol.*, 1902, liv. 1074.
40. Wells, *Chemical Pathology*.
41. Widal, Abrami, et Brulé, *Presse médicale*, 1907.
42. Wright, *Lancet*, Lond., 1902, ii. 11.

IRON IN THE BLOOD[1]

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THE occurrence of iron in the blood was first described by Menghini of Bologna in the year 1747. Since then, the observation of this iron has been made the object of many investigations, and varying methods have been applied for its estimation. Very naturally there is great discrepancy in the views expressed and the results obtained, and it is hoped that the following paper may throw some light on the subject. The object of this research is first of all to make better known an easy and accurate clinical method for estimating both haemoglobin and iron in the blood; and, secondly, to give the results of a series of such estimations upon both normal and pathological individuals with special reference to pernicious anaemia. In this connexion the relation between the amount of iron combined with haemoglobin and the 'free' iron will be considered. It is believed that hitherto sufficient stress has not been laid upon the importance of this relation.

Methods.

For present purposes only those methods need be considered which are suitable for clinical estimations of iron and in which a small quantity of blood is required.

The old method, in which the iron having been treated with hydrochloric acid is reduced with sulphuric acid and zinc and then titrated with $\frac{N}{10}$ potassium permanganate, needs several cubic centimetres of blood and is not accurate.

Neumann's (1) method, which can be used for both blood and urine, is of the same type. In this 5–10 c.c. of blood are necessary, and this fact alone disqualifies it for general clinical application. It gives, however, fairly accurate results. The blood is ashed in a platinum capsule and extracted, and having been reduced, filtered, washed, treated with potassium iodide and acidified with hydrochloric acid, is titrated with $\frac{N}{250}$ thiosulphate of which 1 c.c. = 2 mg. of iron. For further details the reader is referred to the original paper. The method is only considered thus far because some results obtained by it will subsequently come under discussion.

[1] A Thesis presented for the degree of D.M. in the University of Oxford.

One of the earliest colorimetric methods is that described by Thomson (2) in 1855 as suitable for estimating minute quantities of iron in the presence of large quantities of other metals. This was further elaborated by Mackie (3) in 1898. The method depends on the red colour which potassium thiocyanate strikes with ferric salts; the colour so produced by 40 c.mm. of blood previously ashed and dissolved in strong hydrochloric acid is compared with a standard solution of $FeCl_3$ (of which 1 c.c. represents 0·000004 grammes of iron) run in from a burette into a similar quantity of thiocyanate and hydrochloric acid.

The best known method is probably that of Jolles (4). By this 0·05 c.c. of blood is ashed in a platinum capsule and incinerated with potassium bisulphate. The residue is dissolved in hot water and hydrochloric acid is added, The red colour produced by the addition of ammonium sulphocyanide is compared with that struck by a standard solution of iron (0·00005 gramme of iron oxide in 1 c.c.) with a similar amount of sulphocyanide. Cylinders containing the solutions to be compared are placed in a colorimeter and the fluid in the standard column is run out until the colours match.

The method which has been used in this research is a modification of Jolles's. It was first described by Autenrieth (5) in 1910. The apparatus consists of a colorimeter in which the standard colour is in the form of a graduated hollow wedge filled with coloured fluid, the varying thickness of the wedge presenting different depths of colour. By means of a screw at the side the wedge can be moved up and down and accurately matched with the solution to be tested and the value so obtained read off on the scale at the side.

The illustration may perhaps make this clear. The solution to be matched is placed in the small cell A, which is fixed in position alongside the wedge W. The two colours are observed through the eye-piece E. A Helmholtz double plate, H, is used, and thus the two colours are brought into accurate apposition: there is no separating line or dark space between them, and the illumination is uniform and does not depend on the position of the solutions and of the observer's eye.

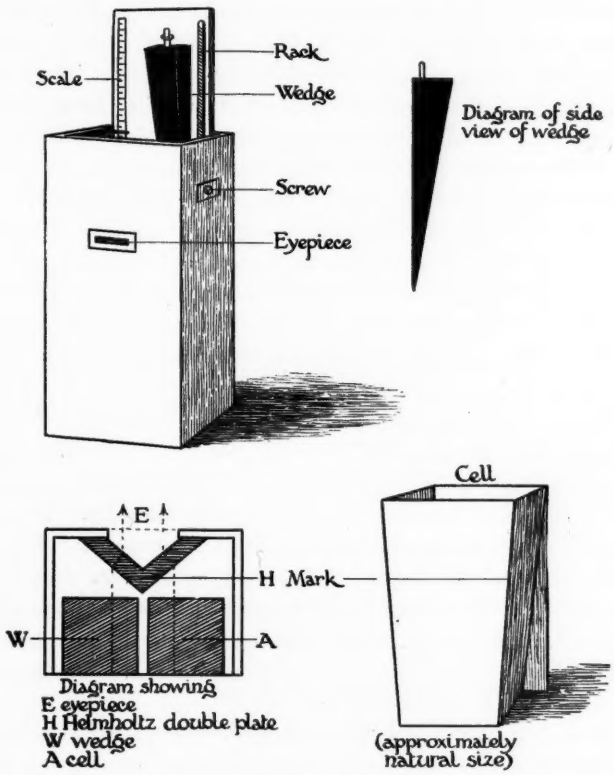
It is claimed that the instrument can be used for a variety of purposes, and wedges displaying different colours are supplied. The author has only had experience of them in connexion with haemoglobin, iron, and creatinine.

For the estimation of haemoglobin the cell A is filled to the mark with hydrochloric acid of about $\frac{N}{10}$ strength and 20 c.mm. of freshly-drawn blood are admixed. Almost at once a clear brown solution (or rather suspension) of acid haematin is formed. The colour does not attain its full depth for about five minutes. The cell having been placed in position is compared with the standard wedge, which contains 'an optically equal and durable solution', the composition of which remains undisclosed. It is not acid haematin, but it forms a perfect match. The instrument has previously been standardized on a normal healthy adult whose red count is about 5,000,000 per c.mm., and whose haemoglobin, using Haldane's method as a rough control, is 100 per cent. or over.

The instrument with which these results were obtained was standardized,

taking the mean of three healthy young adults whose red corpuscles numbered 5,000,000 or slightly over and whose haemoglobin, according to Haldane's method, registered 99, 100, and 105 respectively. Six estimations were made with each of these persons, using varying amounts of blood, and the figures so obtained were found to fall in a straight line when represented graphically.

A graphic curve is supplied with the instrument and gives the values for Freiburg, but it is far better for each person to calibrate his own instrument, since the standard of health in different places varies and the wedges supplied are by no means uniform, while the curve supplied is unvarying.



The advantages of this method over one such as Haldane's are that: (1) It is far more accurate. The arrangements which have been described greatly facilitate the matching of the colours. It is easier to match the tint of a solution against a graduated standard than to dilute the solution to match a uniform standard. The tint of the artificially prepared carboxyhaemoglobin practically never exactly matches the standard: it is usually a great deal more opaque to rays of light. The position of the two tubes and their relative illumination make an enormous difference. In diluting and mixing the blood a certain

proportion is always lost if, as is usual, the tube is inverted with the finger or a cork closing the open end. An error of 15 per cent. has frequently been found in the estimations by this method as compared with the colorimeter. The colorimeter has often been tested with different samples of the same blood on the same day, and has always yielded very level results—a difference of 3 per cent. being practically never met with. (2) It is quicker. The whole operation can be completed in less than two minutes. (3) The acid haematin will keep in its original condition for many days. (4) The instrument is cheap.

By Sahli's method acid haematin is used as the standard, and the blood is diluted with hydrochloric acid to match this standard, as in Haldane's instrument. This obviates a few of the disadvantages of Haldane's method; but the acid haematin standard tends to deposit in time.

It will be well to describe the technique for iron estimation in some detail. A few small modifications have been made and much time may be lost through inattention to minor details. 50 c.mm. of blood are obtained in a pipette (in the case of a person with haemoglobin of over 90 per cent. 25 c.mm. must be taken). The blood is expelled into a platinum crucible which has previously been fused out with fusing mixture and subsequently carefully washed out with boiling distilled water. The pipette is washed out with many changes of distilled water. The liquid is now evaporated to dryness on a water bath in order to avoid splashing, and is then carefully and completely ashed. 0·5 of a gramme of iron-free potassium bisulphate (Kahlbaum) is now added and the mixture is fused. It is important to heat neither too much nor too little. Prolonged heating causes the iron to become insoluble, and probably the iron is reduced to the oxide, for if sodium peroxide be added it is not nearly so readily reduced by prolonged heating. If heating be not carried far enough the excess of bisulphate remains undestroyed and the mass is insoluble in water. The safest point to take is about thirty seconds after all boiling has ceased and when the fusion mixture appears as a collection of uniform white bubbles. The cooled mass containing the iron as ferric sulphate is then brought into solution with boiling distilled water, not more than about 3 c.c. of which must be used. This is important. The solution is transferred to a flask and 3 c.c. of $\frac{N}{2}$ hydrochloric acid are added. Then 6 c.c. of 10 per cent. potassium sulphocyanide are poured into the flask and a pink solution of iron sulphocyanide, varying in depth of colour according to the amount of iron present, is formed. 10 c.c. of methylated ether are added and the flask is shaken up. The colour is extracted forming a bright pink ethereal solution, the full value being obtained in about 5–10 minutes. It is important not to use any ether which contains reducing substances, and excessive evaporation of the ether is to be guarded against. As a matter of fact the loss of volume, amounting to perhaps 1 c.c., makes practically no difference to the figure subsequently obtained. This point has been repeatedly tested. The ethereal solution is placed in the cell A, and is matched against the special wedge provided. In this way a very accurate reading is

possible. The composition of the pink fluid in the wedge is not made known, but it is probably some pigment—not eosin or carbol fuchsin. This wedge has been calibrated in a similar manner to that for haemoglobin, using a standard solution of iron of known strength. This procedure is both tedious and troublesome, since such small amounts of iron are to be estimated. A solution of iron alum is made up in which there is 0·4306 gramme of *dried* iron alum to the litre of $\frac{N}{2}$ hydrochloric acid. Appropriate quantities of this are taken and the values so obtained should fall in a straight line when plotted out graphically. It is wise to perform several control experiments.

Needless to say the materials used—the potassium bisulphate, potassium sulphocyanide, and hydrochloric acid—must all be pure and iron free. They must be carefully preserved from contamination and tested for iron from time to time. Pure distilled water only should be used both for estimations and for washing out the receptacles. It is apparent that the technique of this estimation is not difficult, and if scrupulous care be taken to exclude contamination and avoid loss of substance, accurate and level results are readily obtained. It appears to me to be of considerable advantage that both the iron and the haemoglobin are estimated on the same instrument both for the sake of convenience and also of ensuring uniformity of results.

Historical.

In 1845 Becquerel and Rodier (6) as the result of eleven analyses found in normal males a maximum of 0·063 mg. per cent. of iron in the blood and a minimum of 0·0508 with a mean of 0·056. In females, as a result of eight determinations, they obtained smaller values—maximum 0·057, minimum 0·048, mean 0·051. In 1850 Schmidt (32) published estimations of the total iron varying from 0·0489–0·051. He also found the amount of iron decreased in pneumonia (as a result of four estimations), and in a man aged 39 with arteriosclerosis and dropsy the iron was 0·0347 mg. per cent. In diabetes he obtained a value of 0·058, an increase on his normal figures. Pelouze (8) gave values from 0·0506–0·0537. Jolles (31) using his colorimetric method gave an average of 0·0486 for normal people. Hladik (10) gave a normal value of 0·042, Jellinek (11) one of 0·0527—both using Jolles's method. In 1900 Jolles and Winkler (12) published results with an average of 0·0576 for normal persons, a good deal higher than Jolles's previous results. Jarish, in one case of cholera, obtained a great increase in the total iron to 0·086; but this would follow from the excessive concentration of the blood in this disease. Freund and Obermeyer (13) found a decrease in the total iron in leukaemia. Kobler, in osteomalacia, obtained an increase.

The greater part of the iron of the blood occurs in combination with haemoglobin. It has been found as the result of many analyses that the amount of

iron combined with haemoglobin is practically constant, and this figure has been given by Hoppe-Seyler (14), Ehrlich (15), and Von Jaksch as 0·42 per cent. Hoppe-Seyler's formula is as follows: $Fe = \frac{Hb. \times 42}{100}$, where Fe = per cent. weight of iron and was calculated from dried haemoglobin on the assumption that one atom of haemoglobin combines with two atoms of oxygen. Objections have been levelled against this. The oxygen content of haemoglobin has never been estimated on human beings, and the findings in animals give such varying figures. According to Bunge's (16) results obtained on animals one atom of haemoglobin combines with two to three atoms of oxygen, and Neumeister (9) concludes that in human beings this is also the case. A paper recently published by Rudolf Peters (17) brings forward results which do not support this view. Bohr believes that haemoglobin is not of necessity the same compound at different times and in different persons. It is proposed to take 0·42 per cent. as representing a true value for the purposes of the present investigations.

It has long been known that iron occurs in the blood in some other combination than that with haemoglobin—that in fact the total iron of the blood exceeds the amount which can be accounted for by the haemoglobin, taking the percentage of iron in that compound to be 0·42. Throughout this paper in the tables of results, both original and those of other observers, two columns have been added, the one headed 'Difference', the other 'Ratio'. 'Difference' means the amount of iron in excess of that which is accounted for by the haemoglobin taking the formula $Fe = \frac{Hb. \times 42}{100}$ to be correct. 'Ratio' indicates the proportion between such difference and the total iron. Biernacki (18) made direct quantitative estimations of the iron and at the same time estimated the haemoglobin. He constantly obtained higher results from his iron estimations than could be accounted for by the haemoglobin present. Sometimes twice as much iron was to be found as was to be expected from the haemoglobin. Jolles and Jellinek confirm this. The latter found that in a case of malaria immediately after the paroxysm the haemoglobin fell 10 per cent. whilst the iron remained constant.

A certain amount of discrepancy may be explained by the presence in the blood of iron-free pigments of the nature of lipochromes, &c. For instance, in a case of sulphaemoglobinaemia whose blood was examined the amount of haemoglobin was in excess of what was to be expected from the total iron. These figures will be found in the table on page 191. On the other hand Mackie, using the method which has been described, stated that the total iron of the blood exists in combination with haemoglobin in normal persons. He confirmed this by estimating the iron in the haemoglobin of horses' blood, and considered that such estimations of the total iron furnished the easiest and most accurate method for finding the percentage of haemoglobin. He did not apply this method to pathological conditions of the blood. The following is the average of a number of estimations upon a series of what he terms normal cases,

although in one case the haemoglobin (Gowers) was as low as 40 per cent. and in none was higher than 90 per cent.:

Total iron.	Haemoglobin (Gowers).	Haemoglobin calculated from Fe.	Difference.	Ratio.
0·063	68·4	14·7	0·036	1·7 to 1

0·063 is an extraordinarily high average percentage for iron to correspond with a haemoglobin percentage of 68·4, and the results which he gives do not support his conclusions.

A good deal less work has been done upon pathological conditions of the blood with reference to iron than upon normal persons if we except chlorotics. Biernacki in two cases of mild chlorosis stated that he found the iron content normal. He argued that in chlorosis and other anaemias there is no diminution but a relative increase of haemoglobin, and that other albuminous compounds of the blood are diminished. His figures were:

	Total iron.	Haemoglobin (Fleischl).	Difference.	Ratio.
Normal	0·055	105	0·011	5 to 1
Chlorosis	0·046	60	0·021	2·1 to 1
Chlorosis	0·023	25	0·010	1·8 to 1

In view of these results it is not very clear on what grounds he states that the iron content is 'normal' in chlorosis. These figures show that relative to normal cases the iron content is raised in chlorosis in proportion to the haemoglobin. But his estimations are not considered to be free from error. Ehrlich (15) examined the blood of anaemic persons microscopically and using suitable reagents found that many erythrocytes gave an iron reaction, thus showing that free iron was present not in the form of haemoglobin. He suggested that you can calculate the haemoglobin from the iron in normal people—'a definite proportion between the haemoglobin and the iron content of the blood actually exists'—but not in pathological individuals as Biernacki has said. Elfiri (19), using the method of Jolles, found that the ratio of haemoglobin to iron was not constant in pregnant women.

In a paper read by Brugsch (20) before the Berlin Haematological Society on the iron content of the blood, he concluded that the haemoglobin and the total iron do not present a constant ratio, that the latter always exceeded the iron of the former by a varying amount. In the discussion that followed Rosen and Grawitz assented to his conclusions and agreed that Jolles's method, which Brugsch had used, was absolutely reliable. Otto David (21), in his inaugural dissertation at Bonn, concluded that the iron content of the blood presents a constant ratio to the pigment materials in normal cases, but that this is not so for pathological individuals. In chlorosis and other anaemias the iron content is often raised. In myelogenous leukaemia the iron content is lower than normal, whereas in lymphatic leukaemia this is not the case. In diabetes mellitus the ratio is decreased.

Some Italian observers (22), using Jolles's ferrometer and Fleischl's haemoglobinometer with titrimetric control analyses, investigated the conditions prevailing in the secondary anaemias of malaria, ankylostomiasis, and pellagra. It was found that the iron varied directly with the haemoglobin. Arthur Mayer (23) used Neumann's method for estimating the iron in both blood and urine. He objects to the colorimetric method of Jolles on the ground that there may be a 15 per cent. error. This is supported by Hladik. As an average for five normal cases he gets a total iron value of 0·0515.

Mayer. *Normal cases.*

Case.	Total iron.	Haemoglobin.	Difference.	Ratio.	
1	0·049	90	0·012	4 to 1	
2	0·050		0·011	4·5 to 1	
3	0·050	105	0·0066	7·6 to 1	
4	0·053	94	0·014	3·7 to 1	
5	0·053	100	0·011	4·8 to 1	
Average	0·0515	96	10·8	4·9 to 1	= Average of all five cases.
Average	0·051	94	12·	4·3 to 1	= Average excluding case 3.

These figures will be discussed later. He also examined five cases of chlorosis in which he found the total iron decreased in amount.

Mayer. *Chlorosis.*

Case.	Total iron.	Haemoglobin percentage.	Difference.	Ratio.	Red count.	Colour index.
1	0·017	31	0·014	4·2 to 1	3,262,000	0·50
2	0·034	60	0·009	3·6 to 1	4,100,000	0·73
3	0·038	35	0·024	1·5 to 1	3,940,000	0·44
4	0·041	63	0·015	2·7 to 1	4,160,000	0·75
5	0·043	50	0·021	2 to 1	4,550,000	0·60
Average	0·034	47	0·014	2·8 to 1		

Zumft and Biernacki found that the iron was not decreased in chlorosis in cases of moderate severity. Mayer objects to their results on the ground that the diagnosis of chlorosis was not certain, and that their conclusions are negatived by all previous findings. He also found that the iron in the urine in several cases of anaemia bore an inverse ratio to the iron in the blood. Some more of his figures will be given: first of all two cases of 'anaemia', and then one case of leukaemia splenica.

	Total iron.	Haemoglobin percentage.	Difference.	Ratio.	Red count.	Colour index.
Anaemia	0·038	77	0·006	6·3 to 1	3,310,000	1·16
	0·039	85	0·004	9·7 to 1	3,620,000	1·15
Leukaemia	0·023	50	0·002	11·5 to 1	3,830,000	0·65

All Mayer's figures will be considered in some detail later in the paper.

Rosin and Jellinek (27) have stated that you cannot calculate the haemo-

globin from the iron of the blood, and conclude that the 'difference' may amount to as much as 20 per cent. This is too great a difference to be accounted for by inaccurate estimations of haemoglobin or iron. Mayer has obtained a difference of as much as 50 per cent. (see cases 3 and 4 in his table of chlorosis). Iron is present in the new-born in some other form than haemoglobin, and in quite a considerable amount, e. g.

Total iron . . . 43 milligrammes per 1000 grammes body weight

Haemoglobin iron 10 „ „ „ „ „ „

Therefore, the difference or *non-haemoglobin iron* amounts to 33 mg. This amount diminishes rapidly, and after the sixth day the non-haemoglobin iron remains fairly constant. It is suggested that it is transformed rapidly into haemoglobin owing to the increasing needs of the young organism for red blood cells.

R. Bayer (7) found that nursing women have a decreased amount of iron in their blood when suckling, owing to its appearance in the milk. In a case of pernicious anaemia he found that the milk contained less iron than normal owing to its retention in the blood. Children have less iron than normal in the blood until the end of suckling. Erben (24) analysed the blood in pernicious anaemia and found that although the *total* iron was decreased the iron in proportion to the haemoglobin was increased. He concluded that either the haemoglobin in pernicious anaemia is very rich in iron, or the corpuscles contain iron in some other form than haemoglobin. He found also that the total lecithin was decreased, but that the erythrocytes contained an increased quality as compared with normal blood. This is an interesting point in connexion with the nature of the combination in which the 'free' iron exists. His results were obtained by the ash analysis of several grammes of whole blood, and of corpuscles and serum separately.

Results obtained.

TABLE A. *Normal Cases.*

Cases.	(*a*) Total iron.	(*b*) Haemoglobin percentage.	(*c*) '*Difference*' between iron of (*b*) and (*a*).	(*d*) '*Ratio*' of (*c*) to (*a*).
1	0·052	97	0·012	4·3 to 1
2	0·056	100	0·014	4·0 to 1
3	0·058	100	0·016	3·6 to 1
4	0·048	93	0·010	4·8 to 1
5	0·052	100	0·010	5·2 to 1
6	0·056	105	0·013	4·3 to 1
7	0·052	100	0·010	5·2 to 1
8	0·058	104	0·016	3·6 to 1
9	0·053	93	0·014	3·7 to 1
10	0·060	110	0·014	4·2 to 1
11	0·054	92	0·016	3·3 to 1
12	0·054	98	0·013	4·1 to 1
13	0·056	104	0·013	4·3 to 1
Average	0·0545	99·69	0·0131	4·2 to 1

This consists of thirteen estimations on normal healthy adult males, the lowest of whose haemoglobin values is 92 per cent., with an average of 99·69 per cent.

The highest iron estimation, 0·060, occurs in case 10 with a haemoglobin of 110 per cent.; the lowest, case 4, has total iron 0·048, and haemoglobin 93 per cent. The average, 0·0545, of total iron agrees very closely with the figures of previous observers, but is slightly higher than the average, 0·0515, of Mayer's five cases given on page 186. However, his average haemoglobin percentage is 96 as compared with 99·69 in Table A. The point about this table which should be emphasized is that, although the total iron in normal people follows fairly closely the haemoglobin value, yet it does not do so absolutely, but varies within definite limits. Hence the 'difference' or free iron, i.e. that iron which is not accounted for by the haemoglobin, as shown in column (*c*) also varies. This is clearly shown by the 'ratio'—the proportion which 'difference' bears to the total iron—in column (*d*). The highest figure is 3·3 to 1, the lowest, 5·2 to 1, giving an average of 4·2 to 1.

Mayer's average ratio for all his five normal cases is 4·9 to 1. But his results include one—case 3—which has a very low total iron for a normal person as compared with the percentage of haemoglobin. This naturally results in a correspondingly low ratio, namely, 7·6 to 1. This is so much at variance both with the remainder of his figures and the foregoing in Table A, that it may safely be concluded to be an error.

Excluding case 3, then, his average ratio works out at 4·3 to 1, which agrees fairly well with the ratio of 4·2 to 1 obtained from Table A

TABLE B. *Secondary Anaemia.*

Cases.	(*a*) Total iron.	(*b*) Haemoglobin.	(*c*) Difference.	(*d*) Ratio.	
1	0·023	40	0·007	3·2 to 1	
2	0·014	26	0·004	3·5 to 1	
3	0·027	48	0·007	3·8 to 1	
4	0·016	26	0·005	3·2 to 1	
5	0·022	38	0·007	3·1 to 1	
6	0·035	60	0·010	3·5 to 1	
7	0·023	45	0·005	4·6 to 1	
8	0·034	64	0·008	4·2 to 1	Cirrhosis of the liver and jaundice.
9	0·038	70	0·009	4·2 to 1	Jaundice with enlarged liver.
10	0·029	54	0·007	4·1 to 1	Cirrhosis of the liver and jaundice.
11	0·050	89	0·012	4·16 to 1	Acholuric jaundice.
Average	0·0282	50·9	0·007	3·7 to 1	These figures do not correspond, but represent the average of each column separately.

This table shows the results of a series of estimations on a number of patients suffering from secondary anaemia from different causes. No chlorotics

or other special forms of anaemia are included. The causal agent, as regards the first seven, is haemorrhage, usually post-operative or due to haematemesis, but No. 2 is a case of carcinoma uteri.

Cases 8, 9, 10, and 11 are included in the table chiefly because, first, they present anaemia, and secondly, the figures obtained conform in type to the first seven. They are all cases of cirrhosis of the liver, and were undertaken with the idea of finding out if in a disease characterized by excessive breakdown of haemoglobin there was an excess of iron in the blood. It is evident that such was not found to be the case. All four cases were jaundiced. These results will be specially discussed later on.

It will at once be seen that the figures for iron follow the haemoglobin value as closely as in normal cases, and the 'difference' is depressed in proportion to the decrease in haemoglobin. This is shown by the ratio-average 3·7 to 1, which is slightly higher than in normal cases. The highest figure is 3·1 to 1 as compared with a highest of 3·3 to 1 in Table A.

Mayer gives no clue to the nature of the two cases of anaemia given on p. 186. If regarded of the ordinary secondary type the ratio which has been worked out for them is quite at variance with the results in Table B. And, if regarded as cases of anaemia gravis, they are still more at variance with the results given in Table C. The high colour index is the only fact supporting the latter view.

TABLE C. *Pernicious Anaemia.*

Cases.	Total iron.	Hb.	Difference.	Ratio.	Red cells.	Colour index.	Remarks.
1 ♂	0·023	30	0·011	2·09 to 1	1,050,000	1·5	Normoblasts and megaloblasts present.
2 ♂	0·023	32	0·010	2·3 to 1	900,000	1·7	254 normoblasts and 178 megaloblasts in 200 cells.
3 ♂	0·017	21	0·008	2·1 to 1	875,000	1·3	
4 ♂	0·036	44	0·017	2·1 to 1	1,450,000	1·5	
5 ♂	0·038	53	0·016	2·3 to 1	1,400,000	1·9	Normoblasts present.
6 ♀	0·029	47	0·010	2·9 to 1	1,985,000	1·2	Doubtful case, girl aged 16, normoblasts present.
Average	0·0274	36	0·0124	2·17 to 1	1,110,000	1·58	Excluding case 6.
				2·29 to 1	= Average including case 6.		

In Table C are collected the results of analyses on six cases of anaemia. Five of them are undoubted cases of pernicious anaemia with a small number of red cells, a high colour index, and presenting all the well-known features of this disease. They are all middle-aged males. Case 6, however, is that of a girl of 16 with an enlarged spleen. No enlargement of the liver could be detected, and there was no jaundice or ascites. Her anaemia is not so profound as in the other five cases, but the colour index is high (1·2), and nucleated red cells were found

in her blood in small numbers. No megaloblasts were seen and the differential count presented no abnormal features. In all six cases it will be seen that the proportion of 'free' iron is remarkably high in proportion to the total iron, being least in case 6.

The average ratio of total iron to free iron in the first five cases is 2·17 to 1, and if this be compared with the ratio in simple secondary anaemia (see Table C), which averages 3·7, the marked contrast will be evident. The ratio in case 6 is 2·9 to 1, and if this be included it brings the average ratio to 2·29 to 1; but on account of the reasons put forward above, it is rather doubtful if this case should be regarded as a true pernicious anaemia and be included in Table C. It is not perhaps surprising that in a disease in which there is such a great breakdown of haemoglobin, and in which iron is deposited in the tissues of the body, there should be an excess of free iron in the blood apart from the amount which is combined with haemoglobin.

Ryffel (25) gives the following figures:—

	Normal.		Pernicious Anaemia.			
Liver	0·9	0·08	0·24	0·34	0·57	0·60
Kidney		0·004			0·095	0·35
Spleen	0·18	0·09	0·25		0·29	0·44

The results in Table C are sufficiently striking to prove the presence of free iron in pernicious anaemia and suggest that such estimations may be of value in the diagnosis of doubtful cases.

With regard to the ratio of free to total iron in chlorosis: although for various reasons no such results are being shown in this paper, yet the following remarks may be considered justifiable in this connexion. Mayer's results, as shown on page 186, give an average ratio of 2·8 to 1, approaching in type to that which it has been shown are characteristic of pernicious anaemia. His figures, however, are extraordinarily uneven, as shown by the ratios varying from 1·5 to 1 to 4·2 to 1. I do not think that this point should be taken as proved without a further series of experiments.

There remain a few cases not without interest in which iron estimations have been made, and it is proposed to discuss them separately. First of all there are two cases of anaemia. The one, a case of splenic anaemia in a man aged 27, with enlargement of liver and spleen, ascites, and slight jaundice. In proportion to the haemoglobin the total iron is low, and consequently there is a low ratio, 5·2 to 1. The other, a case of leukaemia splenica, shows a slight decrease in the amount of iron, and consequently a low ratio. This may be considered to confirm the results of Otto David and Mayer in contradistinction to Freund and Obermeyer, who obtained a relative increase in the total iron.

	Total iron.	Haemoglobin.	Difference.	Ratio.	Red cells.	Colour index.
Splenic anaemia	0·037	73	0·007	5·2 to 1	5,000,000	0·73
Leukaemia splenica	0·029	57	0·006	4·8 to 1	2,850,000	0·99
					Myelocytes	30%

It would be unwise to attempt to draw conclusions from isolated cases.

Next will be considered a most interesting case of bronzed diabetes. Two estimations were made at different periods of his disease.

Haemachromatosis.

Total iron.	Haemoglobin.	Difference.	Ratio.
0·046	83	0·012	3·8 to 1
0·052	94	0·012	4·3 to 1

showing very little deviation from what may be considered normal.

Clinical history. A man, aged 44, whose first symptoms of diabetes were noticed in December 1911, was admitted to St. Bartholomew's Hospital on April 17, 1912, in an extremely somnolent condition almost bordering on coma. His urine contained acetone, aceto-acetic acid, and sugar to the extent of 150 grammes in the twenty-four hours. No bile pigments were present. The most noticeable feature of the case was the presence of a bluish-brown patchy pigmentation distributed almost all over his body, being best marked on his legs. No definite date for the commencement of this bronzing could be obtained. He had an irregularly enlarged hard liver, and later on developed ascites. The ascitic fluid when drawn off contained sugar 0·17 per cent. There was no jaundice.

The sleepy condition continued, but on May 2 the iron perchloride reaction was negative in the urine, but sugar was still present to about the same amount. Neither urine nor faeces contained an excess of iron; in fact the amount was below normal. But—and this is the interesting point—iron was present in his skin, which gave a microscopic prussian-blue reaction. The tests of Sahli and Schmidt were positive, thus showing some degree of pancreatic insufficiency; Gammidge's test, however, was negative.

At the post-mortem great wasting was apparent. The pancreas was dark in colour. The liver was markedly cirrhotic and enlarged. Iron was present in large quantities in the liver, giving a most marked prussian-blue reaction, and to a less extent in the spleen and pancreas. There was very little iron in the kidneys. The bile contained a decreased amount of iron. A few points about this case will be discussed later in the paper.

The last case to be considered is one in which very low values for iron were obtained in proportion to the amount of haemoglobin.

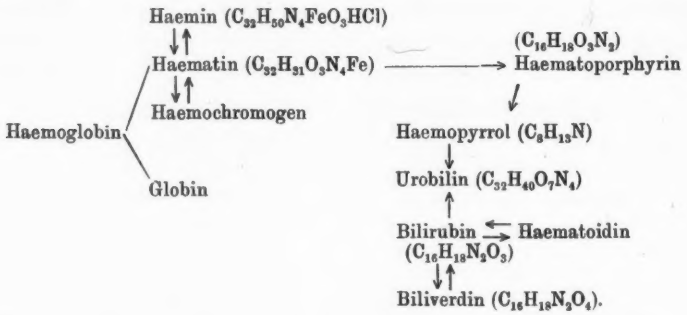
Sulphaemoglobinaemia.

Total iron.	Haemoglobin.	Difference.	Ratio.
0·040	80	0·007	5·7 to 1
0·041	84	0·007	5·8 to 1

Two estimations were performed at different times on a girl suffering from sulphaemoglobinaemia. It has already been suggested on page 184 that a possible explanation may be found in the presence of abnormal blood pigments which do not contain iron.

General Remarks.

The following table may serve to illustrate the relations of haemoglobin and its derivatives:



Haemoglobin consists of two components, a protein *globin* and an iron containing colouring matter, *haematin*. *Haematin* may be experimentally obtained by the action of proteases on haemoglobin, so it is probable that the decomposition of the haemoglobin in the tissues is accomplished in a similar manner by the proteases of the leucocytes, &c. *Haemin* is the hydrochloride of haematin and is an artificially prepared substance. From haematin is split off *haematoporphyrin* with the loss of the iron. *Haemopyrrol* may be obtained from haematoporphyrin. Its common relation to the pigments of blood and bile can be readily seen.

In the breaking down of haemoglobin within the living body the part of the haemoglobin which contains iron is deposited in the liver, spleen, &c., either in simple state or in some organic combination, or both. Some of this acts as a reserve store for the manufacture of fresh haemoglobin in the various organs in which this process takes place, and the iron-free portion is utilized to form bile pigment. After haemorrhages an increased amount of iron accumulates in the liver, but if much blood has been lost the iron content of the liver is decreased, since it has been taken away to form new haemoglobin (Quincke (26)). The iron of the body is not readily parted with. It is excreted in small quantities in both urine and faeces, but the greater part is utilized again and again.

It is not known in what form the iron occurs which is not combined as haemoglobin. Hammarsten states that the nuclein compounds of the blood have iron in combination with them. Ehrlich suggested that iron was present as the albuminate of that metal. Schmiedeberg (28), working on cases of pernicious anaemia, isolated an organic compound of iron—ferratin—from the liver and spleen. He suggested that it was in that form that the 'free' iron of the blood existed. Glikin (29), in the course of his investigations upon a case of polycythaemia rubra with splenomegaly, estimated the phosphates in the blood by extracting the lecithin. He found that no less than 6 per cent. of the iron of the blood was in combination with lipoids. The greater part of the iron deposited

in the organs in pernicious anaemia and in the skin in haemachromatosis is in inorganic combination, though in haemachromatosis some of the pigmentation may be due to haematoporphyrin. It is certain that the iron of the blood not in combination with haemoglobin cannot be in the inorganic form.

Inorganic iron, even in minute quantities, is highly toxic, even more highly toxic than a similar quantity of arsenic in the blood-stream. The free iron in the blood is probably in colloidal form in combination with the protein, e. g. it is well known that egg albumin contains iron. However, as Glikin's results suggest, it is possible that some or all of this 'free' iron is, in combination with lipoid substances, produced by the breakdown of red blood corpuscles, since lecithin is present to the extent of 0·72 per cent. in these cells. Erben (24) showed that lecithin *was present* in increased quantity in the erythrocytes in pernicious anaemia.

Is the free iron of the blood merely an intermediate form between the haemoglobin in the circulation and the iron in the organs of the body—the liver, spleen, and marrow, &c.? Is it, in fact, 'transport' iron? There is a fair amount of evidence, and this is supported by the results given previously, that the free iron is an index of blood destruction. Simpson (30) found that urobilin, whose origin from haemoglobin has been shown, was present in the urine in increased quantity in certain diseases. This increase he found occurred in such diseases as cirrhosis of the liver, pneumonia and other fevers, in anaemias, and after the ingestion of haemoglobin or bleeding into serous cavities. The amount of urobilin was decreased in severe derangement of the liver such as carcinoma. The normal amount of urobilin in the urine is about 10–130 mg. in twenty-four hours, but it might, in the diseases mentioned, be increased to as much as 300–500 mg. in twenty-four hours. Generally speaking, the presence of an excessive amount of urobilin in the urine occurs under two general conditions: after the breaking down of haemoglobin; and as the result of gastro-intestinal disorders. In the former, we should expect that there would be an increased amount of iron in the blood, and this has been found to be the case for pernicious anaemia. In cirrhosis of the liver, on the other hand, it has not been possible to find such excess (see cases 8, 9, 10, 11, Table B) although all four cases were jaundiced. All four were excreting an increased amount of urobilin in the urine. This was very disappointing.

The case of haemachromatosis which I have detailed apparently represents an error of metabolism on the part of the tissues whereby iron is retained instead of being excreted. The man was apparently quite unable to excrete iron. The excessive deposition of iron in the skin may either be due to excessive activity of the liver, or else possibly the liver has ceased to perform its metabolic functions efficiently and the tissues have taken on the task. Probably the same factor which prevents the iron being excreted results in its deposition in the tissues. In this case, if in any, there should assuredly be an increased amount of iron in the blood, but, as the results on page 191 show, this was not so.

Conclusions.

In the course of this work a hundred and twenty-five estimations have been made, and many minor difficulties have been surmounted. Many results were invalidated after several months' work, during which errors of technique were corrected and experience gained. It is confidently believed that the remainder present results as reliable as the method will allow.

It is not asserted that these figures represent the amount of iron in the blood with absolute accuracy to the fourth decimal place, though it is believed that they approximate to it closely enough to support any deductions which have been drawn from them.

Any colorimetric method into which the personal equation is introduced is open to criticism, and where such minute quantities of a material are being estimated error is easy. But in every case presented at least two separate estimations were made on the same day, and in some cases many more. At all events, the results have a comparative value and it is on this aspect that stress had been laid.

As a result of the series of estimations shown it is hoped that the value of Autenrieth's instrument has been proved for the clinical estimation of iron in the blood, and that Biernacki's statement that estimations of the total iron give no true index of the haemoglobin value has been confirmed.

1. That in all individuals there is an excess of iron in the blood over that which is combined with haemoglobin.

2. In normal persons such excess bears a varying ratio to the total amount of iron, but that such variation is, within definite limits, with an average of 4·2 to 1.

3. In simple secondary anaemias the same holds good, but the ratio is on the whole a little higher: average, 3·7 to 1.

4. In pernicious anaemia the ratio is markedly elevated, approaching 2 to 1.

5. In cirrhosis of the liver there is no excess of iron in the blood, and the ratio lies between the normal limits.

My best thanks are due to Dr. Andrewes for the laboratory facilities so kindly placed at my disposal, and to Mr. Wallis for many useful suggestions. I am greatly indebted to Dr. A. E. Garrod for permission to publish details of his cases of haemachromatosis and sulphaemoglobinaemia.

REFERENCES.

1. Neumann, *Zeitsch. für physiol. Chemie*, Strassb., 1902-3, xxxvii. 115.

2. Thomson, cited by Mackie (3).

3. Mackie, 'Iron,' *Lancet*, Lond., 1898, i. 219.

4. Jolles, *Sitzb. d. math.-natw. Kl. d. kaiserl. Akad. d. Wissensch.*, Wien, 1896, xv, Abth. II^b (Method).

5. Autenrieth, *Münch. med. Wochensch.*, 1910, lvii. i. 998.

6. Becquerel und Rodier, *Untersuch. ü. d. Zusammensetz. d. Blutes im gesund. u. krank. Zustande*, Erlangen, 1845.

7. Bayer, R., *Mitt. aus dem Grenzgebiet der Med. und Chir.*, 1910.

8. Pelouze, *Comptes rendus*, Paris, 1865, lxi. 615.

9. Neumeister, *Lehrbuch der physiolog. Chemie*, Jena, 2. Aufl., 1897.

10. Hladik, *Wien. klin. Wochensch.*, 1898, xi. 74.

11. Jellinek, *ibid.*, 775, 778, 796.

12. Jolles und Winkler, *Arch. f. exper. Path. und Pharm.*, Leipz., 1900, xliv. 464.

13. Freund und Obermayer, *Zeitsch. f. physiol. Chemie*, Strassb., 1891, xv. 310.

14. Hoppe-Seyler, cited by Mitulescu, *Zentralbl. f. innere Med.*, Leipz., 1904, xxv. 161, also cited by Mayer, loc. cit.

15. Ehrlich und Lazarus, *Anaemia*, Wien, 1898–1901.

16. Bunge, *Lehrbuch der Physiol. des Menschen*, Leipz., 1901.

17. Peters, Rudolf, *Journ. of Physiol.*, Lond., 1912, xliv. 131.

18. Biernacki, *Zeitsch. für klin. Med.*, Berlin, 1894, xxiv. 460.

19. Elfiri, *Tipografia Rossi-Ubaldi*, 1903; reported in *Folia haematologia*, 1903.

20. Brugsch, *Berliner Haematolog. Gesellsch.*, 1910; reported in *Folia haematologia*, 1910.

21. David, O., *Inaugural-Dissertation*, Bonn, 1908.

22. *Atti del Reg. Instituto Veneto di Scambi*, lxiii; reported in *Folia haematologia*.

23. Mayer, *Zeitsch. für klin. Med.*, Berlin, 1903, xlix. 475.

24. Erben, *ibid.*, 1900, xl. 282.

25. Ryffel, *Journ. of Path. and Bacteriol.*, Camb., 1910, xiv. 411.

26. Quincke, cited by Webster in *Clinical Methods*.

27. Rosin und Jellinek, cited by Mayer, loc. cit.

28. Schmiedeberg, *Arch. f. exper. Path. u. Pharm.*, Leipz., 1894, xxxiii. 101.

29. Glikin, *Biochem. Zeitsch.*, Berlin, 1909, xxii. 461–4.

30. Simpson, *Biochemical Journ.*, Liverpool, 1911, v. 378.

31. Jolles, *Deutsche med. Wochensch.*, 1897, xxiii. 148; *Zeitsch. für analyt. Chem.*, Wiesbaden, 1897, xxxvi. 149.

32. Schmidt, cited by Mayer, loc. cit.

The following books have also been consulted:

Limbeck, *Klinische Path. des Blutes*, 2. Aufl., Jena, 1896.

Schryver, *The Chemistry of the Albumens*, Lond., 1906.

Abderhalden, *Lehrbuch der physiolog. Chemie*, Berlin, 1906.

Hammarsten, *Lehrb. der physiol. Chemie*, 7. Aufl., Wiesb., 1910.

PREMATURE VENTRICULAR BEATS IN HEART-BLOCK

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(From the Royal Hospital, Sheffield)

With Plates 10–13

Most experimental observations on ventricular action in heart-block have been made at the time of, or shortly after, an injury: i. e. under highly artificial conditions. Erlanger and Blackman (3) succeeded in producing chronic heart-block in five dogs and observing the effect of varying conditions on the action of the ventricles: in one of their cases the dissociation was on the borderland between partial and complete.

Clinically the behaviour of the ventricles under varying conditions of rest, exercise, &c., has been observed mainly in cases where the damage is permanent; for complete dissociation, unless transiently produced by a toxic agency, is not often recovered from.

In the present case the rhythmic and conducting functions were unstable, varying from week to week or even from day to day. As might be expected under such conditions, the phenomena observed did not altogether tally with those hitherto described in cases of heart-block. A consideration of the case may help towards the elucidation of problems connected with conduction and rhythmicity.

A brief history of the main clinical features will be given before proceeding to the examination of the tracings.

The patient was a man aged 33, unmarried, who had worked as a slater for several years. He denied both syphilis and rheumatism. About Christmas, 1911, he had an attack of 'bronchitis', and since then had been feeling run down, but continued at his work for a month or two. Eight weeks before admission he had three short fainting fits on three successive days, each attack lasting about two or three seconds. After this he felt worse and discontinued work. Previous to admission he had sudden attacks of shortness of breath with praecordial pain on slight exertion, which quickly passed away on sitting down.

On April 26 he was admitted into the Sheffield Royal Hospital under the care of Dr. Burgess, by whose kind permission I have been enabled to examine and report on the case.

He lay comfortably in bed without dyspnoea. The apex beat was very indistinct, but there was a prolonged systolic lifting of the praecordium nearer to the sternum, with a sudden fall. The cardiac dullness extended from $\frac{3}{4}$ inch on the right to $3\frac{3}{4}$ inches on the left of the mid-sternal line. A prolonged systolic murmur was best heard in the third and fourth spaces just to the left of the sternum, and being traced outwards was lost $\frac{1}{2}$ inch outside the nipple line.

A sharp shock-like second sound was present all over the praecordial area to the left of the sternum. The cardiac sounds were barely audible in the second right interspace.

Polygraphic tracings showed complete heart-block, with very numerous ventricular extra-systoles, giving rise usually to a bigeminy but sometimes to a trigeminy.

A Wassermann reaction, done a few days after admission, was strongly positive. He was given 1 drachm of potassium iodide per diem and kept recumbent.

Dissociation remained complete until May 5, the ventricular rate varying from 52 to 32 per minute. From May 6 to 10 2 : 1 rhythm was present, but after this the dissociation was again complete up to the time of his discharge to the convalescent home on June 10. From this time onward tracings were taken less frequently, but each time up to July 25 2 : 1 rhythm was shown, although on three separate occasions the pulse-rate was reported by the Sister in charge as being between 68 and 75. Since July 15 the rhythm was mainly 1 : 1, with occasional relapses into 2 : 1.

During the whole time of observation exercise has been usually followed by a period in which extra-systoles are very frequent; but whereas at first a slow walk of a few yards was sufficient to bring out a prolonged period of these beats, later on mounting sixty or more steps was followed by so transitory a succession of them that it was difficult to obtain a record of their occurrence.

Polygraph Records.

Figs. 1 and 2 are from a continuous piece of tracing taken on the day of admission. Fig. 1 shows the last five bigeminal cycles before the ventricle

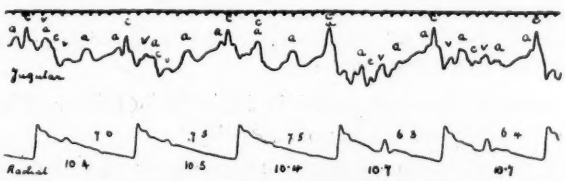


FIG. 1. Shows five bigeminal cycles, the ventricles being completely dissociated from the auricles. The figures below the radial tracing indicate the lengths of the bigeminal cycles in fifths of a second: those above, the lengths of the extra-cycles, also in fifths.



FIG. 2. A continuation of the same tracing immediately after the cessation of the premature beats.

regained the regular rhythm shown in Fig. 2. It will be seen on comparing the two figures that the pauses after all the premature beats are shorter and some of them much shorter than the pauses between the rhythmical beats. The last two

extra-cycles[1] have a length of 6·3 fifths as against about 8·5 for the rhythmical cycles.

This is contrary to all experimental data. Premature beats produced by induction shocks during complete heart-block have been found to be followed by pauses approximately equal to the rhythmical pauses—'the difference rarely ever exceeds one-fifth of a second' (2), (4). The hypothetical explanation of this constancy is often represented by a diagram such as Fig. 3, in which the oblique line represents the anabolic processes.

In the experiments with chronic heart-block in dogs, referred to above, Erlanger and Blackman (3) observed a short series of premature beats occurring spontaneously. On this occasion 'the extra-cycles were always a little longer than the normal periods'.

Experimenting with the perfused heart Cushny (1) found much the same result. He says, 'In this experiment a single extra-systole causes a very slight depression, the interval between the extra-systole and the succeeding beat being

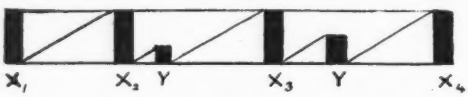


FIG. 3. A diagram to illustrate the usually observed equality of the pause after a ventricular extra-systole to the pause between two rhythmical beats.

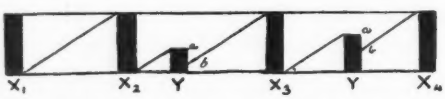


FIG. 4. The distance a–b being constant, and the oblique lines parallel, the distance X_2–X_3 must be equal to the distance X_3–X_4.

1·8 seconds, while the normal period is 1·67. This I have noted repeatedly, although as a general rule there is no such delay.'

There is thus more than one mention of the prolongation of an extra-cycle, but I can find no reference to its shortening, and clinical observations have hitherto been in accordance with experimental.

On the day of admission there was no gradual variation in the lengths of the extra-cycles. In over fifty bigeminies recorded, all the extra-cycles measured approximately either 7·6 fifths or 6·3 fifths (see Fig. 1). This suggests that the extra-systoles were of two varieties, each affecting the rhythmicity in a different way. On other days also the tendency of the extra-cycles to separate themselves into different categories according to length was seen, though here it was sometimes overshadowed by the gradual quickening of the ventricular rate, which will be referred to later.

In the great majority of instances the extra-systole with the longer pause fell early in the bigeminal cycle and vice versa; so that there was great

[1] By an extra-cycle is meant the cycle occupied by an extra-systole and the succeeding diastole. By a rhythmical cycle is meant a ventricular cycle when no extra-systoles are present.

constancy in the length of the bigeminal cycle (about 10·5 fifths). From this it might have been thought that it was the position of the premature beat which determined the length of the succeeding pause; in fact, that the mechanism might be represented by such a diagram as Fig. 4, where a, b is a constant. There were, however, two (possibly three) exceptions present on this day, and on other days the exceptions were more numerous.

Fig. 5 shows in the last cycle (possibly also in the first) an extra-systole falling early after the preceding beat and yet followed by a short pause, so that in this case the whole bigeminal cycle measures only 8·7 fifths, or but little more than the rhythmical cycles as seen in Fig. 2.

Towards the end of Fig. 6 is seen a premature beat falling late and yet followed by a pause of 7·2 fifths, so that the whole bigeminal cycle measures 11·6 fifths. The arterial pressure is raised for a more prolonged period by this

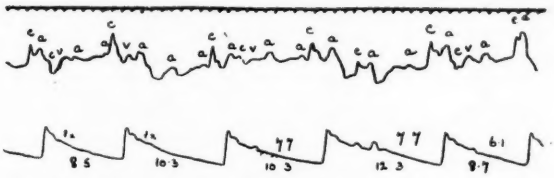


FIG. 5. The last bigeminal cycle shown is very short, owing to a premature beat which has fallen early being followed by a shortened pause.

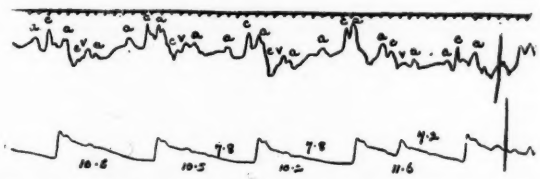


FIG. 6. The last bigeminal cycle in this figure is longer than all the others, owing to a late-falling premature beat being followed by a long pause.

beat than by the beats followed by short pauses (see Fig. 1), and this too seems to mark out a difference in type.

On this day the premature beats ceased abruptly, and the tracing being continued for a short time it was found that there was gradual quickening of the ventricular rhythm: immediately after the extra-systolic period the rhythmical cycles measured approximately 8·5 fifths, about 1 minute later approximately 7·7 fifths, and some 5 minutes later still 5·9 fifths. On all subsequent occasions when premature beats were induced by exercise the ventricular rhythm was found to be slowed for a variable period after the cessation of the bigeminal rhythm, the original rate being gradually restored. Sometimes the gradual quickening was seen through the bigeminal period.

That exercise alone did not cause this slowing was shown by the fact that on two occasions when no extra-systoles were produced by exercise the rate was slightly increased.

This is in accordance with the experimental finding of Erlanger and Blackman (3) that running exercise in dogs with chronic heart-block definitely increases the ventricular rate.

In view of the slowing that takes place the question arises whether the extra-cycles approximate in rate to the rhythmical cycles before exercise. The answer is in the negative: sometimes they were shorter, as in Fig. 7, and sometimes, as is seen by comparing the electro-cardiograms Figs. 17 and 18, they were longer.

If the heart-block was complete the auricular rhythm was never found to be slowed after a period of extra-systoles. On the contrary, that was usually a quickening of rate due probably to the effect of the exercise. On comparing the first and second parts of Fig. 7, it will be seen that the auricular cycles have shortened from 3·5 to 3·0 fifths, and this shortening continued after the cessation of the bigeminies.

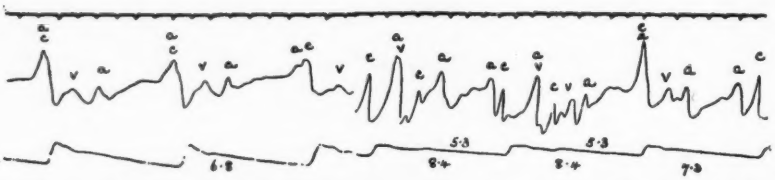


FIG. 7. The first part of this figure shows complete dissociation with a regularly beating ventricle; the second part, taken a few minutes later, shows two bigeminies and an ordinary cycle. The auricular rate is faster in the second part.

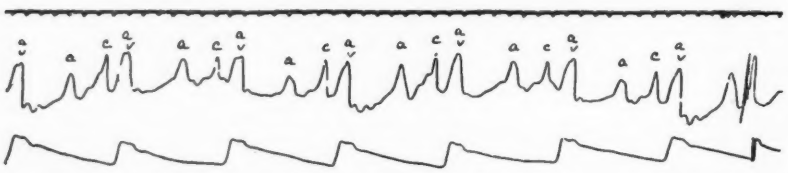


FIG. 8. Shows 2:1 rhythm; the *a–c* interval is 2·5 fifths. One auricular beat in each cycle occurs before ventricular contraction is complete.

Before discussing the above facts it will be well to examine the tracings taken at the time when the dissociation was incomplete, as also the electro-cardiograms.

Fig. 8 shows 2:1 rhythm as it was present for a few days during May and for a considerable portion of June and July. At first sight the three waves seen in the jugular tracing might be mistaken for ordinary *a*, *c*, and *v* waves, but a consideration of the pulse-rate, of the tracing shown in Fig. 9, and of some of the electro-cardiograms renders it clear that there are two *a* waves to each ventricular cycle, the first one of which practically coincides with the *v* wave. The *As–Vs* interval is greatly prolonged, remaining at from 2 to 2·5 fifths for considerable lengths of time, and it is this which causes the occurrence of the next *a* wave before ventricular systole is complete. In the electro-cardiogram Fig. 21, the P wave is seen falling between S and T.

Fig. 9 also shows 2:1 rhythm, but here, instead of the *As–Vs* interval

remaining long, it gradually shortens through five successive cycles, and finally, when it has become under 1 fifth, there follows a single cycle of 1:1 rhythm with the *As–Vs* interval again prolonged. This occurred once only in a tracing taken on May 7, but it recurred with considerable regularity through a large part of one taken on the next day. This improvement in conduction was not however maintained, and two days later dissociation was again complete.

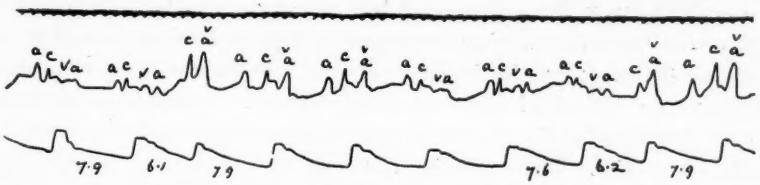
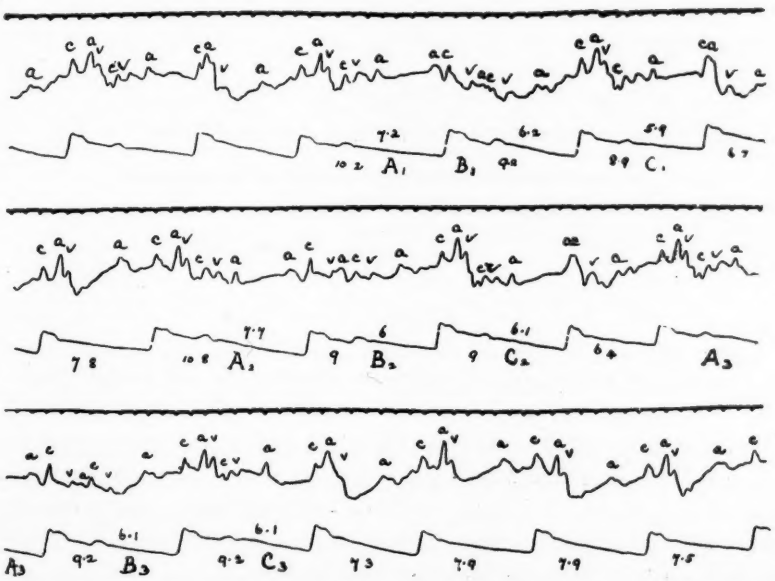


FIG. 9. Shows two cycles of 1:1 rhythm, the remaining cycles being 2:1. Between these two short cycles the *a–c* interval, which is at first long, gradually diminishes in length till it is less than one-fifth of a second.



FIGS. 10, 11, and 12. Taken towards the close of a bigeminal period with 2:1 rhythm; in the latter part of the last figure ordinary 2:1 rhythm is seen. The cycles marked A_1, A_2, A_3 show what is usually seen when a premature beat interrupts the regularity of this rhythm. The six cycles marked B and C are much shortened, the reasons for which are discussed in the text.

On May 7, while 2:1 rhythm was present, the patient was sent for a slow walk of about 30 yards, and this was followed by a period of bigeminal beats lasting perhaps 10 to 15 minutes. Figs. 10, 11, and 12 are parts of a continuous piece of tracing taken at this period. In each of them three successive bigeminal cycles A, B, and C are shown (A_3 is split through the necessity of dividing the tracing). In the latter part of Fig. 12 the regular 2:1 rhythm is

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re-established. The extra-cycles at A_1, A_2, and A_3 are nearly, but not quite, equal in length to the ventricular cycles of the 2 : 1 rhythm, each premature beat being followed by two *a* waves before the next ventricular beat. This slight shortening, when the degree of block is unstable, has its experimental parallel (2). The six extra-cycles at B_1, B_2, B_3 and C_1, C_2, C_3 are however much shorter, each premature beat being followed by only one *a* wave before the next beat. In the three cycles B_1, B_2, B_3 the *a* waves fall late after the premature beats, and this might be the factor determining a ventricular response to these instead of to the succeeding *a* waves; but in the cycles C_1, C_2, C_3 the *a* waves again fall early, so that the next ventricular beats are probably escapes. If this is so, one and the same explanation for the shortened pause will suffice, whether the block be complete or partial. The shortening of the cycles immediately following C_1, C_2, and C_3 appears to be due to the auricular impulse falling earlier.

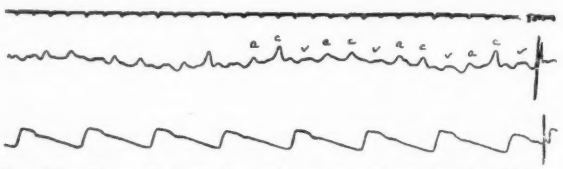


FIG. 13. Shows 1 : 1 rhythm with an *a–c* interval of 1·4 fifths.

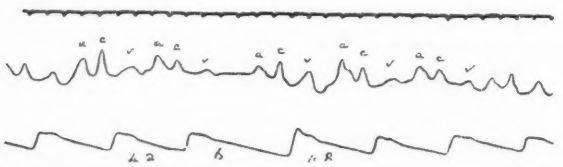


FIG. 14. Taken after exercise a few minutes later than the preceding figure. Considerable irregularity is present with slowing of the average rate. The *a–c* interval is now 1·2 fifths.

The auricular rhythm after the bigeminal period was never found to be slowed; if the exercise was sufficient it was quickened, and on other occasions it remained the same as before the onset of the bigeminies. While the extra-systoles were present this rhythm appeared to be a trifle irregular, the auricular beats next after the extra-systoles falling a little late.

Fig. 13 is from a tracing taken on July 17: it shows the ventricle responding to all the auricular impulses, the *As–Vs* interval being approximately 1·4 fifths.

After ascending about 100 steps it was found that no further dissociation had taken place, the *As–Vs* interval being actually somewhat shorter, but that the whole heart had become slowed and irregular. Fig. 14 is from a portion in which the slowing is less pronounced but the irregularity at its height.

On the next day the slowing after exercise was much more pronounced, but unfortunately a record of its maximum degree was not obtained. Fig. 25 shows the termination of the period of extreme slowing: immediately before this plate was taken, the shadow of the galvanometer string was seen to stand still for

some seconds and then to beat with gradually increasing rapidity. The electrocardiogram indicates that in all probability the extreme slowing was of sinus origin. The patient was a little dizzy at this time, and half an hour later, when he was not under observation, he was obliged to sit down because of a feeling of faintness.

After this experience it was considered unsafe to press the exercise, and no more long pauses were obtained, but the minor degrees of slowing and irregularity were readily obtained. When care was taken to obtain the records at the shortest possible intervals after exercise it was invariably found that the slow irregular period was preceded by a period of extra-systoles. Figs. 15 and 16 show the condition before, during, and after the bigeminal period: before

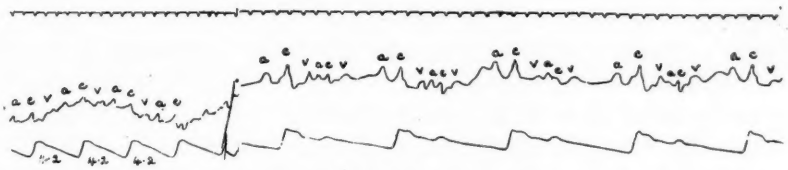


FIG. 15. The first part, taken immediately before exercise, shows regular 1:1 rhythm; the second part, taken about two minutes later, after exercise, a bigeminal period. The average auricular rate in this part is approximately the same as before, but the regularity is disturbed slightly, the auricular beat next after the premature beat falling a little later than expectation. This is best seen in the third bigeminal cycle.

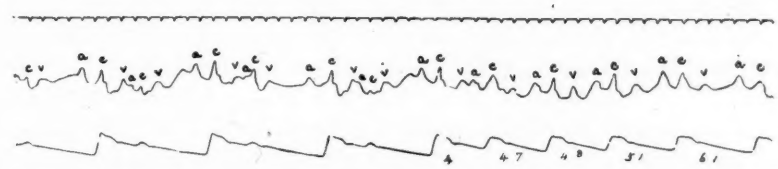


FIG. 16. Shows the termination of the bigeminal period seen above, and the slow irregular sinus rhythm which follows this period.

exercise the rhythm was regular and each cardiac cycle measured 4·2 fifths; after the extra-systolic period the average duration of the first twenty cycles was 5·1 fifths. The bigeminal cycles, of which there were twenty-five recorded, varied in length, but had an average duration of 8·8 fifths, so that the average auricular rate at this time was almost the same as before exercise. On examining the latter half of Fig. 15 it appears that the auricular rhythm is not quite regular, the beats after the extra-systoles appearing a little later than expectation.[2] This suggests that exercise had tended to quicken the sinus rate, but that each extra-systole had a depressant effect on the sinus node.

On one occasion, July 24, when 1:1 rhythm was present, a bigeminal period produced by exercise was followed by 2:1 rhythm for some 10 minutes before the re-establishment of the original rhythm. This dislocation into a higher grade

[2] It is unlikely that the premature beats seen in this figure are auricular in origin, since the *a–c* intervals are so short, and also because of the known frequency of premature ventricular beats in this patient.

of dissociation by means of extra-systoles is a not infrequent experimental result, and further examples of it are shown in the electro-cardiograms Figs. 21, 22, 23, and 27; but the point to notice is that when the conduction was thus affected by the extra-systoles, there was no slowing of the auricular rate: each auricular cycle with the 1:1 rhythm before exercise measured approximately 3·8 fifths, and with the 2:1 rhythm after the bigeminal period the measurement was approximately 3·4 fifths. With the return of the 1:1 rhythm the auricular rate was again slowed to what it had been before exercise (3·8 fifths).

Electro-cardiograms.

Fig. 17 is an example of the curve present with complete dissociation and a regular ventricular rhythm. The ventricular complex indicates that the impulse has arisen in the bundle and travelled by both branches. It is, however, of a somewhat peculiar type: the R variation being very small and the T large. This type of complex was invariably present under the above conditions (complete heart-block with regular ventricular rhythm) whether the ventricular rate was fast or slow: curves obtained with the rate as low as 32 and as high as 45 per minute showed only slight variation:—with the slower rate the R was a little smaller and the S a little larger than in the figure.

Fig. 18 shows a period of bigeminal beats. The curve was taken a few minutes after Fig. 17, the patient having in the meantime ascended some steps. The extra-cycles are here seen to be longer than the rhythmical cycles of a few minutes before. The complex of the first beat of each bigeminy indicates its supra-ventricular origin, but here the type differs from that seen in the preceding figure, and although there was some slight variation, the first beats of a bigeminy never showed a complex approximating in type to that seen with the regular ventricular rhythm. The complex of the second beat of each couple indicates a contraction starting in the right basal portion of the ventricles.

Fig. 20 shows three bigeminies and one single beat. It was taken with a tighter string than the preceding curves and in consequence all the movements are lessened, but taking this into consideration the second and third couples are seen to be approximately the same as those shown in Fig. 18. The premature beat of the first couple is approximately of the same type as seen in Fig. 17. The time-marker was unfortunately not working while this curve was taken, but a fair idea of the time may be gained by observing the auricular beats. It will be seen that the distance BC is considerably shorter than the distance CD, whereas the distance AA much more nearly approximates. The cause of this variation in length of pause will be discussed later.

Fig. 21 shows 2:1 rhythm. When the ventricles were responding to auricular impulses the complex was always of this type, with a deep S. Fig. 22, taken a few minutes later after exercise, shows four auricular beats to each bigeminal cycle, and Fig. 23 shows the transition from this to 3:1 rhythm.

Dislocation to a higher degree of block after extra-systoles was seen more than once. Fig. 27 shows 3:1 rhythm which was produced in this way from a previous 2:1 rhythm.

Figs. 24, 25, and 26 show 1:1 rhythm. They were taken at short intervals of time, the interval between the first two being occupied by exercise. They show the irregularity and slowing of the whole heart that has occurred after the exercise. The period of maximum slowing, as seen by noting the shadow of the string, occurred just before Fig. 25 was taken.

Discussion.

1. *Slowing of rhythm after a period of extra-systoles.* In this patient, when the block was complete, slowing always took place in the ventricular rhythm: the auricular rate was either increased or, if the exercise had been slight, remained the same as before. When however 1:1 rhythm was present slowing and irregularity of the whole heart, auricles as well as ventricles, was the consequence.

With intermediate degrees of dissociation (2:1) the auricular rate was, as with complete block, increased or the same as before. Its regularity, however, appeared to be slightly disturbed during the period of extra-systoles, the auricular beat after each premature beat falling a little later than expectation. (The ventricular rhythm, being dependent on the auricular, was slowed or quickened according to whether a higher grade of block was produced by the extra-systoles or not.)

Cushny (1), experimenting with the perfused heart and complete dissociation, found that a rapid ventricular rate produced by induction shocks was always followed by slowing of the ventricular rhythm; the amount and duration of the slowing being dependent on (*a*) the condition of the heart in general, its temperature and oxygen supply and the length of time it had been exposed, (*b*) the duration and (*c*) the rate of stimulation. He found that a 10 per cent. increase in rate was sufficient to produce a prolonged slow stage. The extra-systoles in the present case, when the block was complete, produced at the lowest a 12 per cent. increase in rate, so that the subsequent slowing might be accounted for in this way.

When we come to the auricular slowing present with the lesser grades of block, the explanation is not so easy. Here the ventricular rate of the bigeminal period was not greater than the preceding auricular rate, and the dependence of the auricular slowing upon the state of conduction seems to forbid the application to this particular case of Cushny's suggestion that the metabolites of contraction overwhelm the pacemaker.

All that one can say at present is that ventricular extra-systoles have in this case a depressing effect on the pacemaker of the heart, providing that the conducting path is sufficiently open. It seems at least probable that the

depression of the ventricular pacemaker by extra-systoles, when the block is complete, is also dependent on the state of conduction at the moment in the lower reaches of the bundle.

The curious phenomenon present on July 24 seems to indicate that the burden of conduction has also a depressant effect on the rhythmicity of the sinus pacemaker.

2. *What is the cause of the shortened extra-cycle?* Lewis (5) has described a case in which the pauses after certain auricular extra-systoles arising near the pacemaker were shorter than the rhythmical pauses. He suggested that this shortening was due to stimulation of the pacemaker by the premature beats. The same explanation may apply in the present case, but it seems unlikely in view of the fact that, as seen in Fig. 20, a right-sided beat is followed by a shorter pause than a beat with a complex similar to the rhythmical ventricular beats. If, on the other hand, a poorer state of conduction lessens the depressing effect of an extra-systole, then one would expect the right-sided beat to be followed by a shorter pause.

3. *Aberration.* Under this title Lewis has described variations in the type of the electric complex of supra-ventricular beats in the same individual. This variation only occurs in cases where the conducting function is impaired, and he ascribes the phenomenon to different degrees of conduction impairment in the various arborizations of the bundle. He shows an electro-cardiogram of an asphyxiated cat in which purely right-sided beats were evidently supra-ventricular in orgin.

In the present case several different types of complex were seen. In Fig. 19 minor variations in type are seen from beat to beat. The type seen in Fig. 17 corresponds rather closely to one of the aberrant types shown by Lewis (Fig. 25, column (*a*) II, in the original paper): that seen in Figs. 21 to 27 is similar to another shown by Lewis (Fig. 25, column (*c*) II).

Conclusions.

A case is presented showing the following phenomena:

1. Complete and prolonged dissociation alternating with periods of 2:1 rhythm, and finally leading through 2:1 into 1:1 rhythm.

2. Ventricular extra-systoles appearing usually after exercise.

3. When the dissociation was complete, the period of extra-systoles was followed by slowing of the ventricular rhythm, the auricular rhythm remaining unaffected: on the other hand, when 1:1 rhythm was present the rhythm of the whole heart became slow and irregular after a bigeminal period.

4. The pauses after the premature contractions were often considerably shorter than the intervals between the rhythmic ventricular beats; the shortening is referred to the momentarily depressed state of conduction.

5. When partial dissociation was present the onset of extra-systoles sometimes led to a higher grade of dissociation.

6. 'Aberration of the supra-ventricular impulses' was present.

My best thanks are due to Dr. Thomas Lewis for his kind and ready assistance in the interpretation of some of the points of the case, and to Professor Macdonald for kindly placing at my disposal the galvanometer and other apparatus in the Physiological Laboratory, University of Sheffield.

REFERENCES.

1. Cushny, *Heart*, Lond., 1911–12, iii. 257.
2. Erlanger, *Amer. Journ. Physiol.*, 1906, xvi. 160.
3. Erlanger and Blackman, *Heart*, Lond., 1909–10, i. 177.
4. Hering, *Archiv für die ges. Physiol.*, Bonn, 1905, cvii. 108.
5. Lewis, *Heart*, Lond., 1911–12, iii. 279.

DESCRIPTION OF FIGURES.

Electro-cardiograms.

PLATE 10, FIG. 17. Shows complete dissociation with a regular ventricular rhythm. The ventricular complex shows a very small R and a large T. (The time-marker in this and the next two figures is marking sixths of a second; in the remaining figures it is marking fifths.)

FIG. 18. Taken a few minutes later, after exercise, it shows a regular series of bigeminies with dissociation, the premature complexes being all such as are given by contractions starting in the right and basal portion of the ventricles.

FIG. 19. Shows a bigeminal series. The premature beats of the second and fourth couples are right-sided, but the remainder show complexes similar to the idio-ventricular beats. There is some variation in the sizes of the R, S, and T variations from beat to beat.

PLATE 11, FIG. 20. Shows three couples and one single beat. Two of the premature beats show a right-sided complex, the other shows one similar to that shown by the regularly beating dissociated ventricle. The length of the pauses should be noted.

FIG. 21. Shows 2:1 rhythm. The ventricular complex was always of this type when the ventricle was responding to an auricular impulse.

FIG. 22 and PLATE 12, FIG. 23. Taken shortly after the preceding figure. They show the effect of extra-systoles in producing a higher grade of block.

FIGS. 24 and 25, and PLATE 13, FIG. 26. Show 1:1 rhythm. The first was taken before exercise, the other two after. Slowing and irregularity of the sinus rhythm is seen in the last two.

FIG. 27. Shows 3:1 rhythm, which followed a bigeminal period, the rhythm before this having been 2:1.

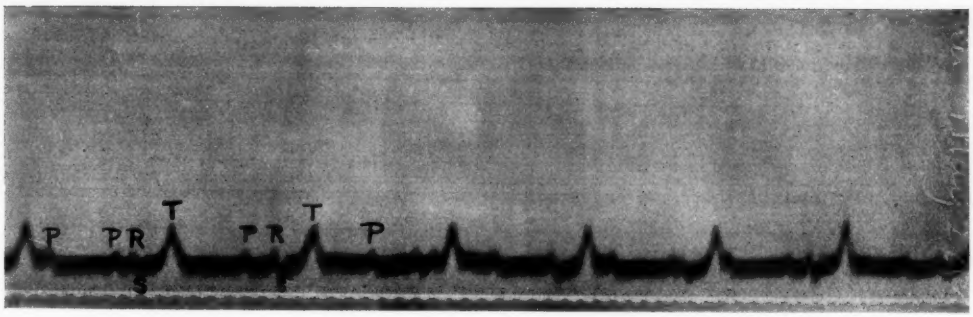


FIG. 17

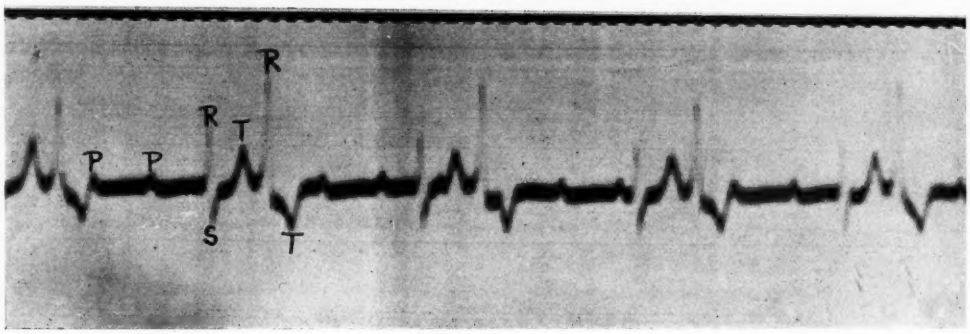


FIG. 18

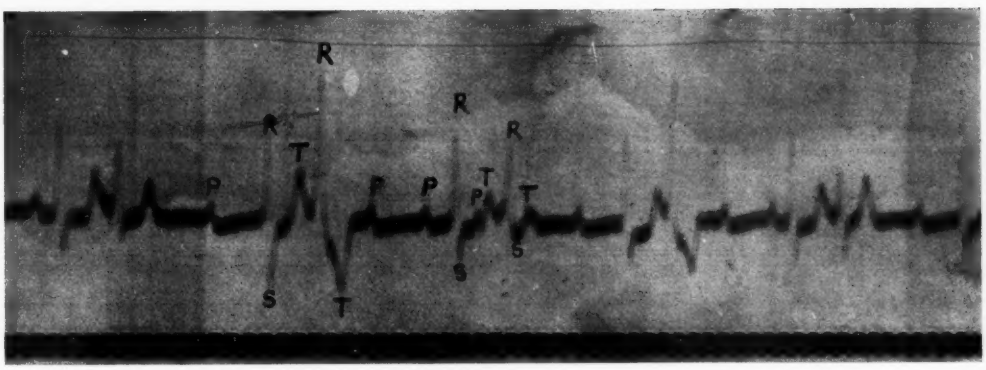
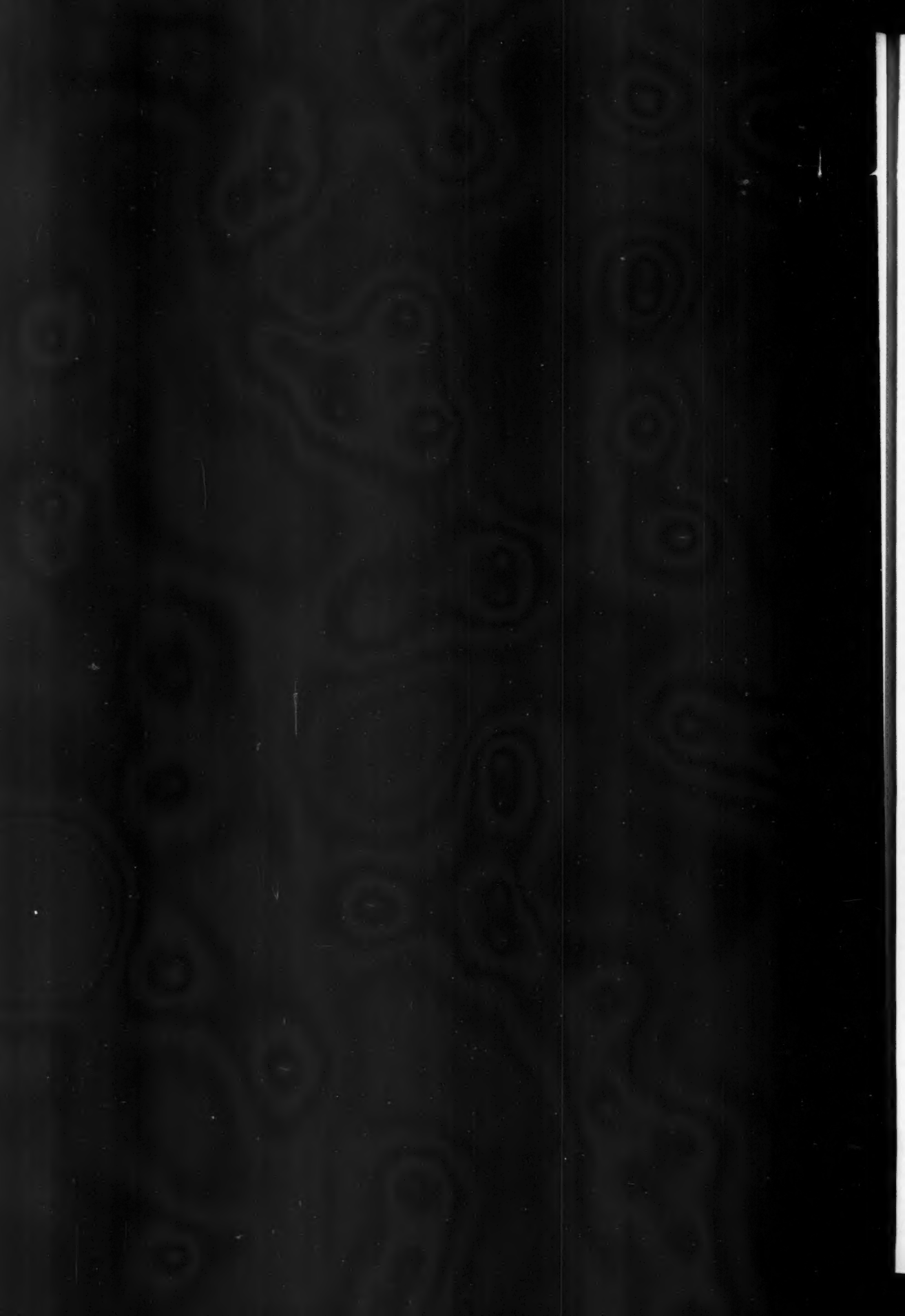


FIG. 19



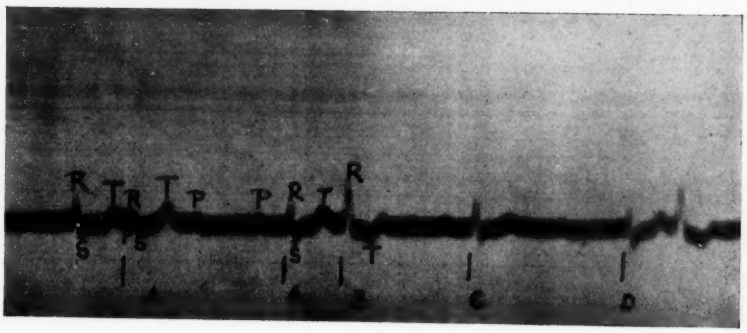


FIG. 20

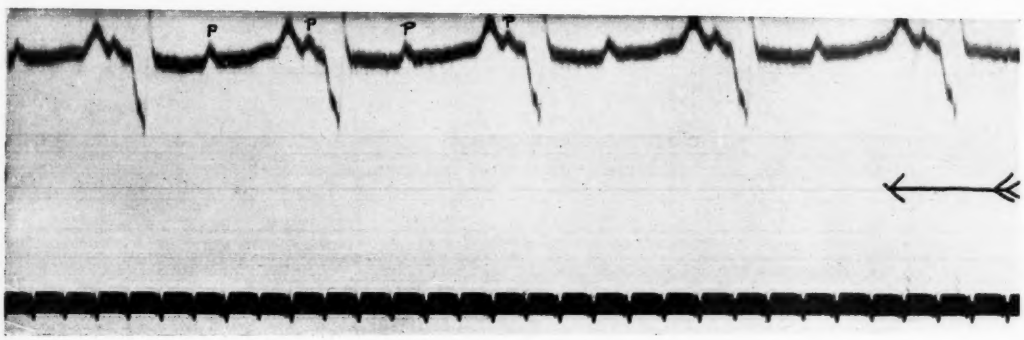


FIG. 21

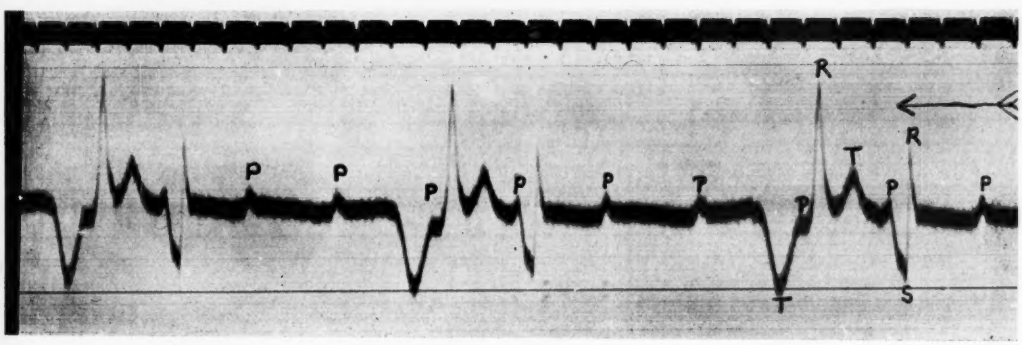


FIG. 22

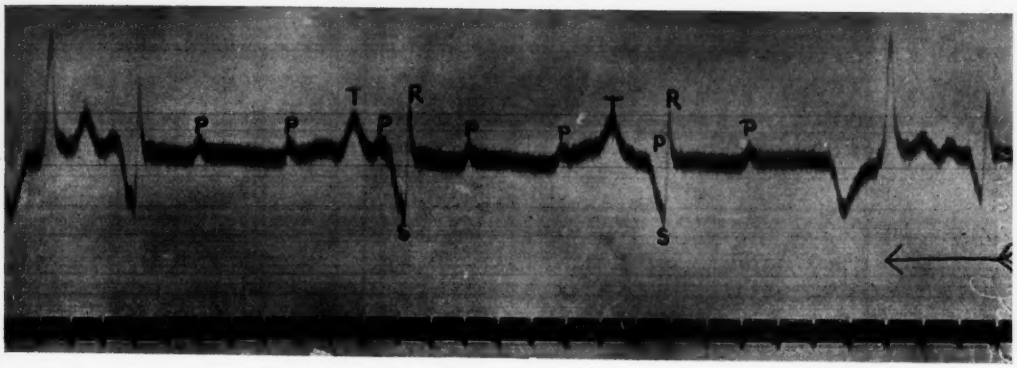


FIG. 23

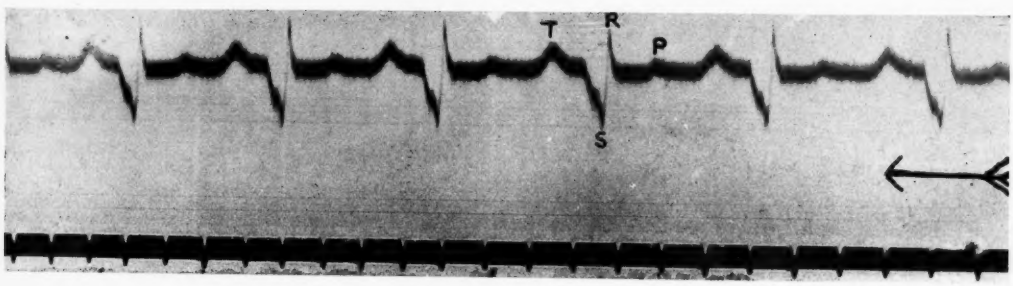


FIG. 24

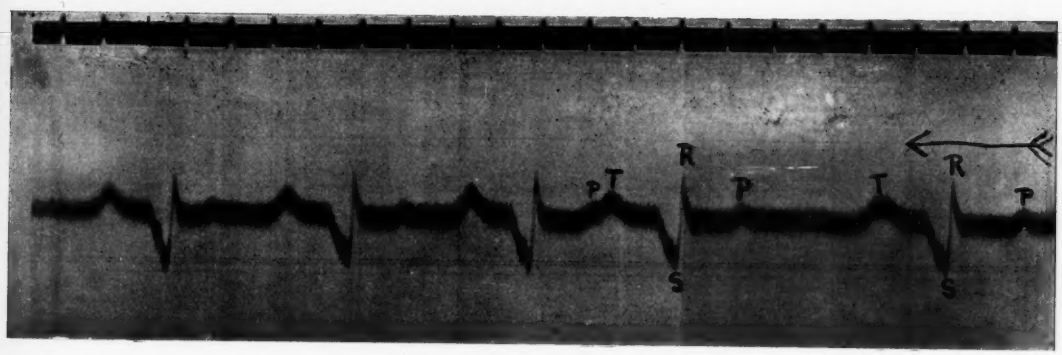


FIG. 25



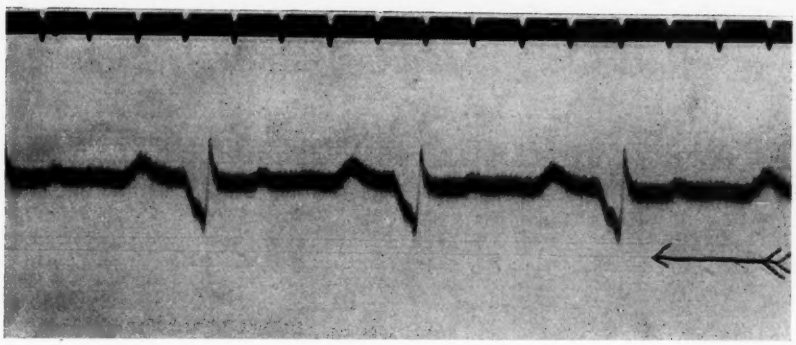


FIG. 26

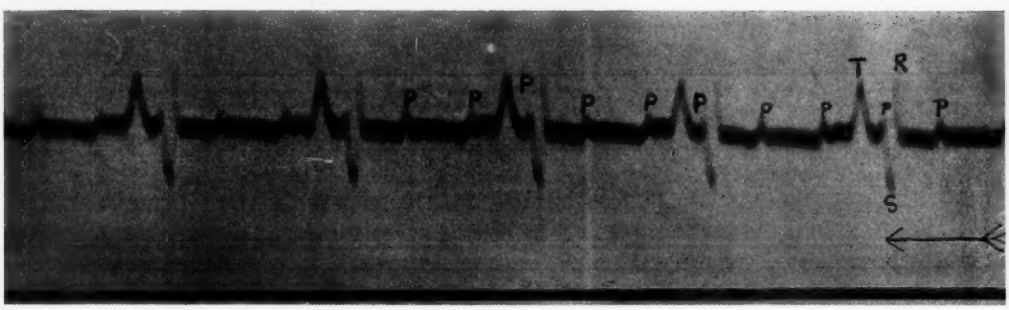


FIG. 27



OBSERVATIONS ON AURICULAR AND NODAL (?) EXTRA-SYSTOLES

By E. E. LASLETT

THE observations which are brought together in this paper are based on records obtained during the past three years from three patients. They relate to (1) The rhythmical appearance of auricular extra-systoles; (2) The relation of auricular extra-systoles to auricular fibrillation; (3) The occurrence of a peculiar and unusual form of coupled rhythm which is always introduced and sometimes terminated by one or more couples, both beats of which arise in the auricle; (4) The occurrence of auricular and nodal (?) extra-systoles with a succeeding pause shorter than that separating two normal beats.

The Rhythmical Appearance of Auricular Extra-systoles, including Coupled Rhythms of Auricular Origin.

In a coupled rhythm the second beat of the couple is usually a ventricular or nodal extra-systole. In a recent paper Cowan and Ritchie (1) state that they have not been able to find a record of an undoubted instance of a prolonged bigeminal rhythm due to a regularly recurring auricular extra-systole, although a transient rhythm of this nature has been recorded by Lewis (7). Recently (5) I published an account of a woman aged 72 who had had brief attacks of paroxysmal tachycardia observed in the summer of 1910. The attacks were associated with the frequent occurrence of auricular extra-systoles. Later the attacks of tachycardia ceased and the pulse became almost constantly of the bigeminal type. From that time to the present (September, 1912) she has been seen on the average once a week, and the pulse has constantly presented the same irregularity when the patient is standing or sitting. After a hurried movement the pulse temporarily quickens and becomes regular, and also soon after lying down the coupled rhythm tends to become less constant, but on the whole it is correct to say that the bigeminy is persistent and has been so for over two years. The curves in Fig. 1 were obtained when the patient was recumbent, and it will be noticed that at the end of the curves the coupled rhythm is interrupted by two normal beats. Both beats of each couple are preceded by an *a* wave, and the *a–c* interval is the same for both, namely, about 0·15 to 0·16 second. In each couple the pause is from 0·1 to 0·15 second short of being fully compensatory.

[Q. J. M., Jan., 1913.]

The nature of this irregularity calls for some consideration. It was not possible to obtain a satisfactory cardiogram in this patient and consequently the *a–c* interval must be taken as the index of the true *As–Vs* interval. Now for a pulse-rate of 70 the *a–c* interval is somewhat short, but the shortening is not beyond the limits of known variation for beats arising in the normal pacemaker. It is therefore probable that for the first beat of the couple the normal sinus-auricle sequence holds.

The nature of the second beat is not, however, at once so certain. In the first place one can probably exclude sinus arrhythmia. This form of irregularity is rare in elderly people, and such a type as this, which has persisted with so little variation for two years, is scarcely conceivable. Strong evidence in favour of the extra-systolic nature of the second beat of the couple may be found in the fact that at one time the regular bigeminy was frequently disturbed by the occurrence of two premature beats in succession with a shortened pause, and that occasionally the second beat of a couple appeared earlier than usual and was then represented by a much smaller wave in the radial curve (Fig. 4 in the above paper). If this is so the 'true bigeminy' of Wenckebach (12) may be excluded as an interpretation of the rhythm.

The *a–c* interval of the second beat is practically the same as that of the first, and it is well known that the *a–c* interval of an auricular extra-systole is usually increased owing to increased presphygmic delay. This, it may be suggested, is evidence that the extra-systole has arisen in the neighbourhood of the node. It is, however, to be noted that the premature beat in this case occurs late, and as evidenced in the radial curve is stronger than an extra-systole usually is. It is therefore probable that there is little or no increase in the presphygmic period, which may account for the absence of an increased *a–c* interval. On the whole the balance of evidence is in favour of interpreting the coupling as due to the regular occurrence of an extra-systole which arises in the main mass of the auricle.

The curve in Fig. 2 illustrates the regular occurrence of two successive premature beats after every second normal pulse-beat. The curve was obtained from a woman aged 40, whom I have attended off and on for some years. She has no apparent organic heart lesion, but she suffers from some degree of anaemia. The irregularity was observed at a time when she was complaining of breathlessness and palpitation on exertion. I saw her at my house one morning and found that the pulse was irregular, with two full beats, followed by two quick and feeble ones. The irregularity continued for some minutes, but finally disappeared as she recovered from the exertion of her walk to see me. No record was taken then, but in the afternoon I saw her at her own home. I got her to mount the stairs quickly and then lie down, and a curve was taken immediately. At first the pulse was quick and fairly regular, and then it settled down into the rhythm depicted in the figure. It will be seen that the regularity of the sequence was occasionally interrupted by the substitution of a single premature beat instead of two. The rhythm ceased abruptly after a few minutes and the

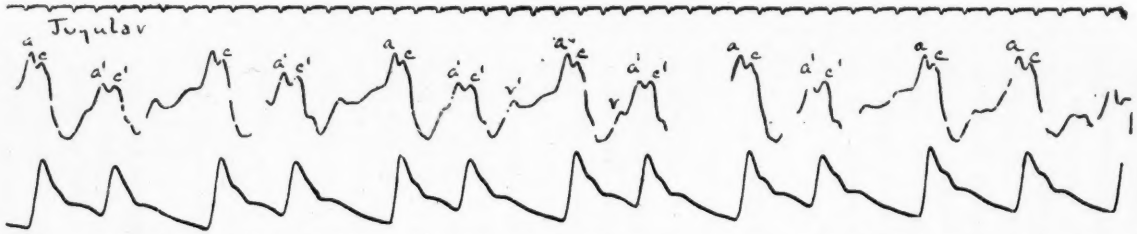


FIG. 1. Shows a bigeminal rhythm due to the regular occurrence of auricular extra-systoles. The bigeminy is interrupted at the end by two normal beats.

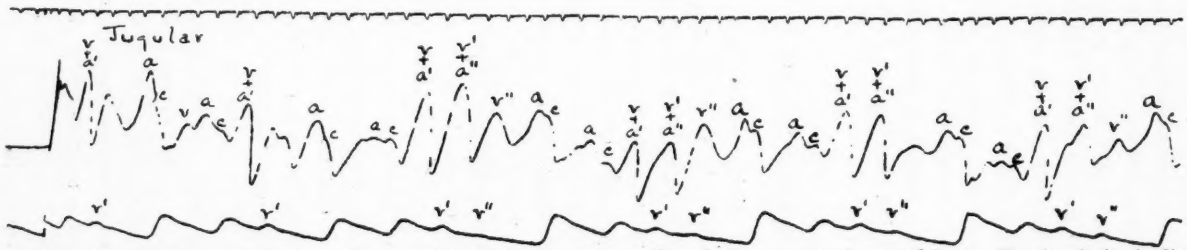


FIG. 2. Shows the regular occurrence of two successive auricular extra-systoles after every second normal beat. The regularity is disturbed at the beginning of the curve, where only a single extra-systole appears instead of two. The *a* wave of the extra-systole is superimposed on the preceding *v* wave.

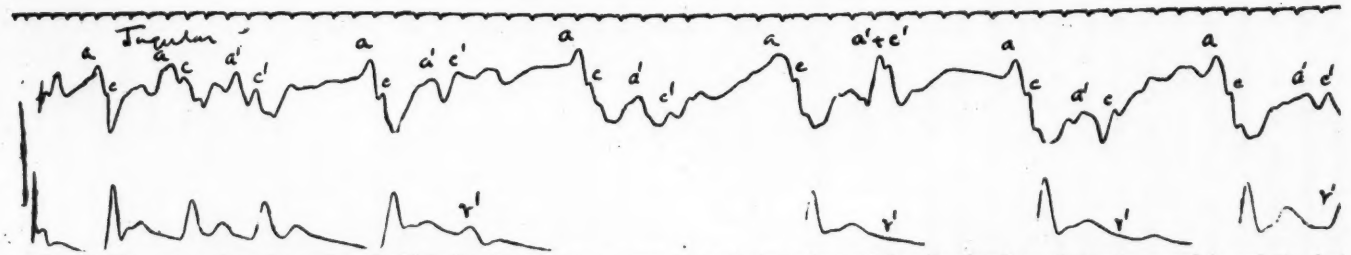


FIG. 3. Shows a series of couples of which the first three are due to auricular extra-systoles, the fourth probably to a nodal, and the last two to auricular extra-systoles. The large wave in the fourth couple is premature. The extra-systole of the fifth couple is not represented in the radial, the peak in the curve probably being due to an instrumental fault.

pulse became quite regular and remained so. Although the patient remained under observation for some weeks I did not succeed again in observing this form of irregularity.

The premature beats appear to be of auricular origin, the *a* wave of each being superimposed on the preceding *v* wave. That they are extra-systoles is certain, because they are feebly represented in the radial curve, they occur at a much more rapid rate than the normal beats, they are separated by equal intervals of time, and lastly, when there is only one premature wave, it occurs at the same interval after the preceding normal beat as the first beat of the triple rhythm. As *a* is superimposed on *v* one cannot accurately determine the *a–c* interval, but from the appearance of the combined wave it is probably increased. The pause after the single premature beat is approximately the same length as that following the two in succession and is not fully compensatory. It is remarkably constant.

The Relation of Auricular Extra-systoles to Auricular Fibrillation.

The curves illustrating the remaining sections were obtained from a man aged 24, whose case was referred to in a recent paper (6) on the induction of sinus arrhythmia by digitalin. It is necessary only to state here that he was first examined during an attack of paroxysmal tachycardia. The pulse was not quite regular, but very rapid on the whole, frequently reaching 170–80 per minute. A curve is reproduced in the paper referred to (Fig. 9). The jugular pulse showed no auricular wave in the usual position, and it was stated that it was probable that the auricle was in fibrillation, although the pulse for short stretches simulated a regular tachycardia arising from a single focus. This view is rendered practically certain by a recent paper by Lewis and Schleiter (8). The day after he was first seen the normal sinus sequence had returned and the pulse was 80 per minute on the average. The heart's action was, however, very irregular, and it has remained so up to the present time, nearly a year. The irregularity is due mainly to the frequent occurrence of auricular extra-systoles, with sinus arrhythmia of high grade at times. At one period, as will be mentioned later, a coupled rhythm was frequently observed. For a few weeks after the cessation of fibrillation the extra-systoles occurred not only singly but also in groups, two, three, up to five in succession (Fig. 4).

The patient has since improved to this extent that a presystolic murmur, heard for a few weeks after the attack of tachycardia ceased, has disappeared and the heart sounds have since appeared free from murmur, and also that multiple successive extra-systoles have become comparatively rare. Two in succession are occasionally observed, but for the most part they now appear singly. These however continue to appear at frequent intervals, so that when the patient is erect the intermingling of quick and slow beats is so marked as to suggest the irregularity due to auricular fibrillation. Notwithstanding this he appears to be well and is able to carry on his arduous work.

Although this patient had not been under observation before the onset of fibrillation and the transition from this to the normal sinus sequence was not observed, the case is important as affording further evidence of the connexion between premature auricular contractions and auricular fibrillation, and the frequent occurrence of multiple successive extra-systoles is of special import in

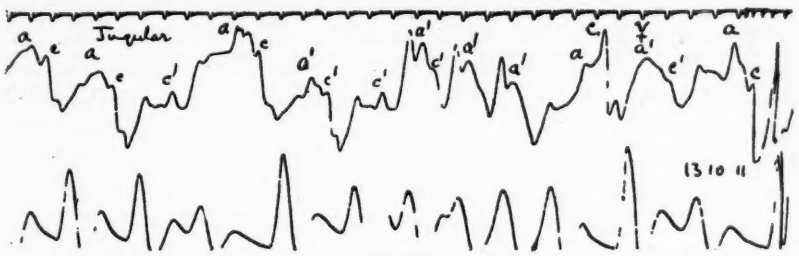


FIG. 4. Shows a series of five auricular extra-systoles in succession. The succeeding pause is not longer than that after the single extra-systoles in the figure.

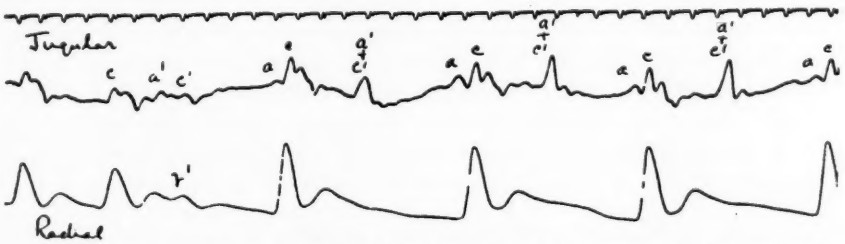


FIG. 5. Shows a series of couples of which the first is due to an auricular extra-systole. The combined wave of the next extra-systole is slightly premature. The pause after the fourth is not fully compensatory.

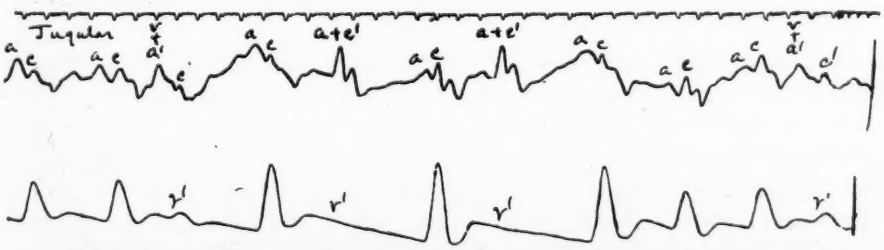


FIG. 6. Shows a series of three couples, of which the first is due to an auricular extra-systole. The last two are due to ventricular or nodal extra-systoles. The compensatory pause of the first couple is short, that of the others is full.

view of their known intimate relationship to paroxysms of regular tachycardia. The subject has been studied by Mackenzie (11), Hewlett (4), and particularly by Lewis (9), whose work has demonstrated the close connexion between the three grades of heterogenetic impulse formation, single and successive extra-systoles, paroxysms of regular tachycardia, and auricular fibrillation.

A Coupled Rhythm of Unusual Form.

For a few weeks after the resumption of the sinus sequence a coupled rhythm was frequently observed. It was invariably introduced by one or more couples, both beats of which arose from the auricle (Figs. 5 and 6). In the following couples a single or two-peaked wave occurred in the jugular pulse simultaneously with the upstroke of the cardiogram of the second beat. It is expressed thus because the second beat of the latter couples was never represented in the radial curve, while the second beat of the auricular couples was represented by a distinct wave. So constant was this difference that it became easy to separate the two forms from an inspection of the radial curve alone. In connexion with this distinction it may be observed that the cardiogram of the auricular premature beat was as a general rule distinctly broader and better sustained than that of the second beat of the remaining couples.

The prominent single or two-peaked wave in the jugular pulse curve appeared most commonly at the time an auricular systole would be expected,

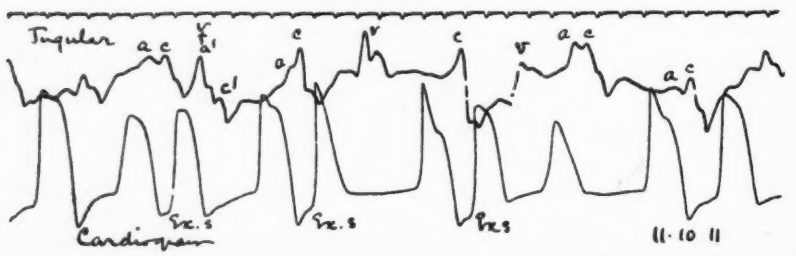


FIG. 7. Shows a series of three couples, the first due to an auricular extra-systole, and the next two due to ventricular or nodal extra-systoles. The pause after the third is shorter than the interval between the first two heart-beats, which are normal. The heart rate is slowed after the last couple.

which would suggest that it was due to a ventricular extra-systole appearing rather late and coinciding practically with the normal auricular systole. As evidence against this interpretation two features may be noted. In the first place, the single large wave sometimes appeared slightly but distinctly before the normal auricular wave was due. Again, the compensatory pause of the auricular premature beats was invariably short of full, while that of the second beat of the remaining couples was sometimes full but in other instances short. Indeed, on many occasions, as will be presently considered, very short couples were noticed, so that the prominent combined wave was much nearer to the succeeding normal auricular wave than to the preceding. These short couples appeared isolated at the end of a coupled rhythm, or, as observed in several instances, in the middle without disturbing the succession of coupled beats. Small variations in the length of the couples might be explained by the presence of sinus arrhythmia, but in many instances (Figs. 7, 8) the shortening was too great to be accounted for in this way. Short couples of this type when they appeared isolated, or at

the end of a coupled rhythm, were almost invariably followed by slowing of the sinus rate for one or two beats. Ventricular extra-systoles, on the contrary, do not affect the sinus rhythm. On these grounds it appears probable that some at least of these premature beats arise in the A–V node or its immediate neighbourhood.

From an examination of numerous cardiograms of the coupled rhythm it appears that the second beat of each couple occurs at approximately the same time after the preceding normal beat, whether it arises in the auricle or elsewhere, and whatever may be the length of the compensatory pause. That is to say, the coupling is fairly accurate.

In two instances a series of couples was also terminated as well as introduced by one or possibly two couples in which both beats arose from the auricle (Fig. 3); and in one instance a couple of auricular origin appeared in the middle of a series of nodal or ventricular origin.

I have considered this form of rhythm at some length because it does not appear to have been previously described, so far as the literature available to me shows, and its very frequent appearance in this patient was a striking phenomenon. Moreover, it may prove to be important in the explanation of the mechanism of coupled rhythms in general. The subject is a difficult one, and it is not proposed to discuss the various theories advanced, but it may be pointed out that the view held by Cowan and Ritchie, that one of the factors in maintaining a coupled rhythm is a prolonged diastole, hardly finds support in this case, where a shortened couple was frequently interpolated in the middle of a series.

Extra-systoles, Nodal and Auricular, followed by pauses which are shorter than the regular Pulse Periods.

The former have been already alluded to in the foregoing sections, and the reasons given for regarding the premature beats as arising from the A–V node. Two examples are reproduced in Fig. 8. From the form of the jugular wave due to the extra-systole it may be concluded that the right auricle has contracted as well as, and simultaneously with, the right ventricle. In the upper curve the combined wave appears prematurely, while in the lower it appears at about the time the normal auricular contraction would be due. The pause separating the combined wave from the next following auricular wave is much shorter than the pulse period immediately preceding the premature beat, and is too short to be accounted for by the presence of sinus arrhythmia. That the following beat is of sinus origin is probable from its height in the radial curve, and from the fact that the a–c interval is not increased, as would be expected were it due to an auricular extra-systole. This view is further confirmed by the occurrence of a shortened couple of this type, which is immediately followed by a couple of the same nature apparently but followed by a compensatory pause (Fig. 9).

In all the examples of shortened couples of this type hitherto observed the extra-systolic period has been followed by depression of the sinus rhythm. This will be again referred to.

The curves in Fig. 10 and that in Fig. 11 illustrate the type of auricular extra-systole which is followed by a pause shorter than that separating the normal beats. The occurrence of this form of extra-systole was of very frequent



FIG. 8. Shows two examples of nodal extra-systoles followed by a shortened pause. In the first the combined wave appears prematurely, but not in the second. The first succeeding pulse period in each instance is lengthened.

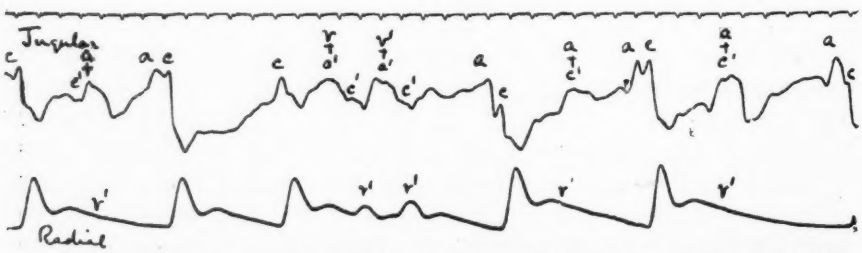


FIG. 9. Shows in succession a shortened couple probably due to a nodal extra-systole, a normal pulse period, two successive auricular extra-systoles, a short couple, and a couple with a long pause. The two last are probably due to nodal extra-systoles, as the combined wave in the last occurs earlier than the midpoint between the normal auricular waves.

occurrence in this patient, and it has persisted up to the present time. In view of the rarity of this type and in the absence of electro-cardiographic evidence it is necessary to consider whether any other interpretation can be given of the phenomenon. In the first place, as already considered in connexion with the nodal extra-systole, the following beat might be an auricular extra-systole. The same arguments suffice to reject this view, namely, the full representation in

the radial curve, the absence of an increased *a–c* interval, and the occurrence of a shortened couple of this form at the beginning of a series (Fig. 11). Or again, can the premature beat be regarded as an interpolated ventricular extra-



FIG. 10. Shows three examples of auricular extra-systoles followed by a pause much shorter than the normal pulse period. Slowing of the sinus rhythm after the extra-systoles is most marked in the first two curves.

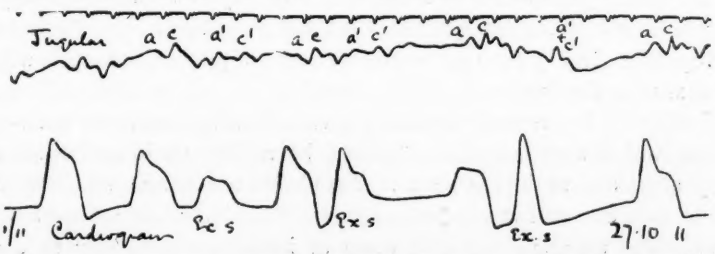


FIG. 11. Shows a series of couples of which the first two are due to auricular extra-systoles. The pause after the first is $\frac{1}{10}$ sec. less than the preceding normal pulse period.

systole? The jugular pulse with its clear indication of a preceding auricular contraction negatives this view. Moreover, an interpolated period exceeds a normal pulse period only by the amount of the increase of the *a–c* interval

following the premature beat. In the examples figured there is no increase of the *a–c* interval, and the couples are too long to admit of this explanation, unless one admits that the extra-systole constantly happens to appear at the precise time when the sinus rhythm is slowed. A still more important argument against such an interpretation is to be found in the considerable variation in the length of the pause from marked shortening, as in Fig. 10, up to pauses which are just less or equal to the normal pulse period. The pause in Fig. 11 is one-tenth of a second less than the preceding pulse period.

As in the case of the nodal extra-systole, in nearly every instance where an auricular extra-systole of this type occurs there follows sinus slowing for one or more beats. Many times this slowing is very marked, so that the first normal pulse period subsequent to the extra-systole is only slightly shorter than the couple itself. There was in this patient at times marked sinus arrhythmia of the irregular type which is independent of respiration. An occasional coincidence of the appearance of an extra-systole with sinus slowing is admissible, but the almost constant association of the two suggests that the depression of the sinus rhythm is in some way dependent on the appearance of the premature beat.

The pause after an auricular extra-systole is usually not fully compensatory. The explanation suggested by Cushny and Matthews (2) is that the premature beat retrogresses to the pacemaker where the stimulus material is discharged. A new impulse is formed at the usual rate, and the next beat follows the extra-systole at an interval equal to the normal pulse period plus the time taken for the extra impulse to travel back to the pacemaker. But in many cases the pause, though not fully compensatory, is too great to be accounted for in this way, and Cushny (3) has recently suggested that the increased length of the pause may be accounted for 'if the impulse from the auricle not only discharges the pacemaker but also in certain conditions depresses it'. His suggestion is based on the observation that artificial stimulation of the isolated ventricle depresses its rhythmicity and thus temporarily slows it, the extent of the depression being dependent on the duration and rate of the stimulus. Lewis (7) has, however, shown that the pause at the termination of a paroxysm of auricular tachycardia, if of moderate duration, is approximately the same as that after a single auricular extra-systole. In Fig. 4 the pause after the series of premature beats is not longer than that after the single one.

Lewis (10) has recently described a case in which auricular extra-systoles occurred which were sometimes followed by a long pause and sometimes by a very short one, as in the above. The electro-cardiogram was, however, the same in each case and was indistinguishable from that of the normal beat. The extra-systoles therefore probably arose in immediate proximity to the pacemaker. To explain the short pause Lewis suggests that 'the extra-systole stimulates physiological impulse formation at the point at which it arose, so that the succeeding physiological impulse is formed more rapidly than usual'.

There is, however, a difficulty in applying this suggestion to the case where what is believed to be a nodal extra-systole is followed by a much shortened

pause, because the extra-systole has arisen from a focus in the junctional tissues while the next following auricular systole has started from a different focus, presumably the normal pacemaker. If it be not granted that these extra-systoles arise in the $A-V$ node, and in the absence of electro-cardiograms an element of doubt must be admitted, the difficulty still remains; for in that case a ventricular extra-systole must coincide with a normal auricular contraction, and that leaves the early appearance of the next normal beat unexplained, because a ventricular extra-systole does not of itself affect the sinus rhythm.

The almost constant slowing after the extra-systoles with a shortened pause, whether these are auricular or nodal, seems to be significant and can hardly be a coincidence. One is tempted to suggest that the premature beat may in some instances be, so to speak, interpolated, so that the stimulus material at the pacemaker is not actually discharged, but its rate of formation is merely slowed. The difficulties of interpretation are however very great, and at the present time it would seem that no one mechanism has been imagined which will satisfactorily account for all the facts.

Conclusions.

An instance of coupled rhythm is described in which the second beat of each couple is due to an auricular extra-systole. This has persisted for two years.

In another patient, suffering from anaemia, the regular occurrence of two successive auricular extra-systoles after every second normal beat was observed after exertion.

In a third patient, on recovery from an attack of auricular fibrillation, very frequent auricular extra-systoles, both single and multiple, were observed. The relation of auricular extra-systoles to paroxysmal tachycardia and auricular fibrillation is commented on.

In the same patient a coupled rhythm was frequently present in which the second beat of the introductory couples was always, and that of the terminal couples occasionally, due to an auricular extra-systole, while the second beat of the intermediate couples was either a ventricular or in some instances probably a nodal extra-systole.

Both the auricular and nodal extra-systoles were sometimes followed by a pause which was shorter than the normal pulse period.

The nature of the pause after an auricular extra-systole is discussed, and it is suggested that occasionally an auricular or nodal extra-systole may be interpolated with simultaneous depression of the sinus rhythm.

REFERENCES.

1. Cowan and Ritchie, *Quart. Journ. Med.*, Oxford, 1910-11, iv. 55.
2. Cushny and Matthews, *Journ. of Physiol.*, Lond., 1897, xxi. 213.
3. Cushny, *Heart*, Lond., 1911-12, iii. 257.
4. Hewlett, *ibid.*, 1910-11, ii. 107.
5. Laslett, *Quart. Journ. Med.*, Oxford, 1910-11, iv. 295.
6. Laslett, *ibid.*, 1911-12, v. 377.
7. Lewis, *Heart*, Lond., 1909-10, i. 262.
8. Lewis and Schleiter, *ibid.*, 1911-12, iii. 173.
9. Lewis, *Mechanism of the Heart-beat*, Lond., 1911.
10. Lewis, *ibid.*, 1911-12, iii. 279.
11. Mackenzie, *Diseases of the Heart*, Lond., 1908.
12. Wenckebach, *Arrhythmia of the Heart* (Snowball's translation), Edinb. and Lond., 1904.

EXCEPTIONAL TYPES OF SLOW HEART ACTION

By THOMAS LEWIS [1]

(Cardiographic Department, University College Hospital Medical School)

With Plates 14 and 15

Case I. G. K., a man aged 62, was admitted to the City of London Hospital for Diseases of the Chest on March 9, 1912, complaining of shortness of breath and cough, which had troubled him at times during the previous three or four years.

Family history. His father and mother were both dead. His three brothers were dead: one died of rheumatic fever, one of 'heart disease', and one of 'congestion of the lungs'. One sister was alive and well. The patient was married and had ten children alive and well.

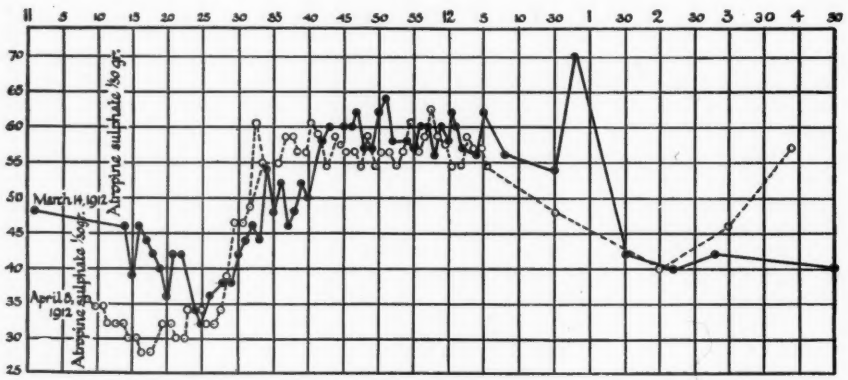
Previous illnesses. He had measles when a child. He had suffered from a cough during the winter months for the last six years. There was no history of acute rheumatism or chorea.

Condition on admission to hospital. The patient was a well-built, healthy-looking man. There was considerable visible pulsation in the neck with each heart-beat. The heart's impulse was not palpable. The deep cardiac dullness extended $1\frac{1}{4}$ and $5\frac{1}{4}$ inches to the right and left of the mid-sternal line respectively. A slight systolic bruit was present at the apex. The sounds over the other valve areas were faint. The heart was slow (40 per minute) and somewhat irregular in action. The radial pulses were equal. There was considerable thickening of the radial arteries. The liver was not enlarged. There were numerous rhonchi over both lungs, and they were conspicuous at the bases, where some crepitations were also heard. There was neither ascites nor oedema of the ankles, but the patient stated that he had noticed swelling of the left leg occasionally. The systolic blood-pressure (Riva-Rocci) was 168 mm. Hg.

Progress. The patient continued in the condition in which he was admitted for several days, and the pulse-rate remaining slow, on March 14, $\frac{1}{50}$ grain of atropin sulphate was injected subcutaneously at 11.13 a.m., and continuous polygraph tracings were taken for fifty-six minutes. The pulse-rates were calculated from strips of curve of half-minute duration in the majority of readings, the pulse-rate being originally 48 per minute (see Chart). At first a slight retardation of rate occurred. This was followed about twenty minutes after the injection by an increase of rate. The heart-rate became accelerated to 64 beats per minute, but did not go beyond this limit; the pulse became regular. By 1.30 p.m. the pulse-rate had returned to its previous slow rate. Subsequently the pulse-rate remained slow. On April 8 a subcutaneous injection of $\frac{1}{30}$ grain of atropin sulphate was administered, and a continuous tracing was taken for fifty-eight minutes following this injection, and the pulse-rates per minute calculated as before. On this occasion also a slight retardation of rate occurred within the first ten minutes of injection, and this was followed about twenty-two

[1] Working under the tenure of a Beit Memorial Research Fellowship.

minutes after the injection by an acceleration of heart-rate. At the same time the patient complained of a dry feeling in the throat. The greatest acceleration was to 62 beats per minute, and within two hours of the injection it had almost returned to its original slow rate (48 per minute). The heart maintained this low speed of contraction during the three months he was in hospital. The evening rate was usually somewhat faster than that of the morning. On May 2 he was allowed to walk down four flights of stairs, spend a half-hour in the grounds, and return to the wards. On this evening the pulse-rate was 56 per minute, and each day it was observed that similar exertion produced the same effect. The fastest rate thus observed was 64 per minute, except on a solitary occasion (May 16), when a rate of 80 per minute was attained. The general physical signs remained unaltered, but the exercise produced a certain amount of dyspnoea. No drug of the digitalis group was given at any time during his stay in hospital.



A chart constructed from continuous polygraphic curves taken from Case I. It shows the effect of two atropin injections, given on March 14 and April 8 respectively. Up till 12.10 the time scale is one division to the minute, afterwards it is two divisions to fifteen minutes.

To sum up, while the usual pulse-rate was 40–48 per minute, after a period of three months, the period of observation, it not infrequently fell below these rates: the lowest rate reached was 26. Rates of over 48 were only observed after atropin injection and exercise.

For the clinical notes of this case and the observations upon the action of atropin I am indebted to Dr. Agassiz, resident medical officer at the City of London Hospital.

Graphic records. In most of the polygraphic curves taken from this patient each arterial pulse-beat was accompanied by a venous wave of the plateau form, the latter being regularly preceded by a single *a* wave (Fig. 1). The corresponding electro-cardiographic curves showed a normal sequence and normal P summits. The slow heart action was therefore usually of uncomplicated sinus origin (Fig. 11). The slow rhythm, as has been stated, was usually fairly regular, but from time to time irregularity occurred. Under these circumstances the irregularity, as portrayed by the venous and electro-cardiographic curves, was also of sinus origin (Figs. 1 and 11); the irregularity was parallel in auricle and ventricle; each ventricular summit, wherever placed, was preceded by an auricular summit of constant form. Here and there in the polygraphic curves the

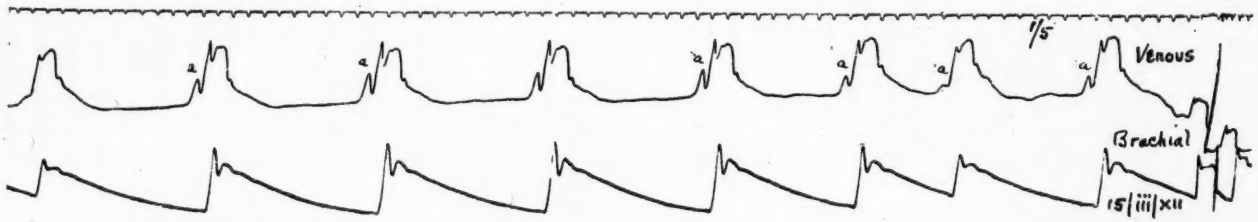


FIG. 1. A polygraphic curve from the jugular vein and the brachial artery, showing a slow and irregular action of the whole heart. The breathing was held.

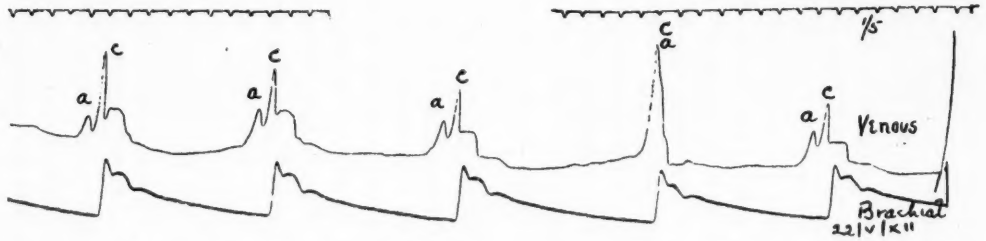


FIG. 2. A polygraphic curve from the same case as Fig. 1, showing four beats of normal origin and a beat of nodal origin, the latter occurring after the longest pause.

mechanism was seen to alter abruptly, and large venous waves, evidently the result of simultaneous contraction of auricle and ventricle, appeared. These might be isolated (as in Fig. 2) or in short groups (as in Figs. 3 and 4). As a general rule they occurred after relatively long pauses. Thus the longest pause in Fig. 2 is the only pause which is followed by a venous wave of this kind. In Fig. 4 the large venous waves start after the longest pause. In Figs. 3 and 4 the usual sequence follows the shortest pause. The reason for the changes will be obvious. There are two active centres of impulse-formation; one lies in the sino-auricular region and produces the sequential beats, the other lies away from it and is ectopic; the latter produces a slower rhythm than the former. For instance, in Fig. 2 the ectopic centre produces but a single effective impulse, and it gives rise to a response only after a rest of unusual length. The first ectopic beat of Fig. 4 may be explained in the same and customary manner. As a general rule, the ectopic rhythm, once developed, increased in rate. This is clear in Figs. 3 and 4. The new centre obeys the customary law in producing its 'rhythm of development'; its activity, once awakened, is enhanced. Thus it happens that the pauses between certain of the ectopic beats may be eventually shorter than the pauses between the sinus beats (as in Fig. 3). Although the examples given illustrate these relations between impulse-formation in the two centres, yet in a few curves exceptions could be found, and these exceptions probably resulted from an irregularity in the rates at which impulses were built up at the two points.

The explanation which alone seems adequate to explain these successive simultaneous contractions is that they have been let loose from a common centre; in short, that we have to deal with transient nodal rhythm. For the auricular and ventricular contractions in any cycle have precisely the same time relations to each other, although the individual cycles have varying lengths. Coincidence of auricular and ventricular contractions, the former originating in the old pacemaker, the latter in the ventricular pacemaker (idio-ventricular beats), is hardly to be thought of in the presence of this irregularity.

The electro-cardiograms, corresponding to these polygraphic curves, are illustrated by Figs. 12, 14, 15, and 16. The ventricular complexes of Fig. 15 are alone found; the closest comparison between these ventricular complexes and those of the normal periods fails to reveal the slightest trace of auricular representatives buried in the former. The comparison may be made most satisfactorily in the first two cycles of Fig. 14, in which the last nodal beat of a series is shown. Yet we know from the polygraphic curves that auricular and ventricular beats started simultaneously. The conclusion seems justified that the auricular representative is of abnormal form and that it is concealed by R.

A comparison of these electro-cardiograms and experimental ones confirms these explanations.[2] Auricular representatives may be present, but may be so concealed that the electro-cardiograms require a very close comparison with simultaneous myocardiograms before these representatives are revealed.

[2] Unpublished observations.

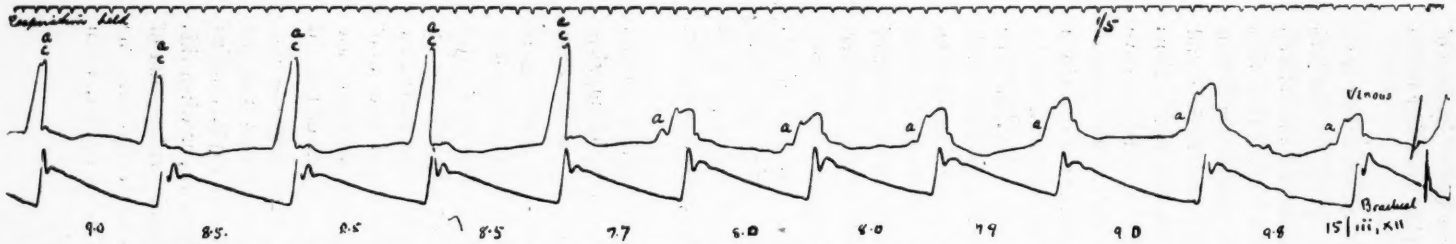


FIG. 3. Polygraphic curve from the same case as Fig. 1, showing the end of the period of slow nodal rhythm and the re-establishment of a slightly irregular sino-auricular rhythm.

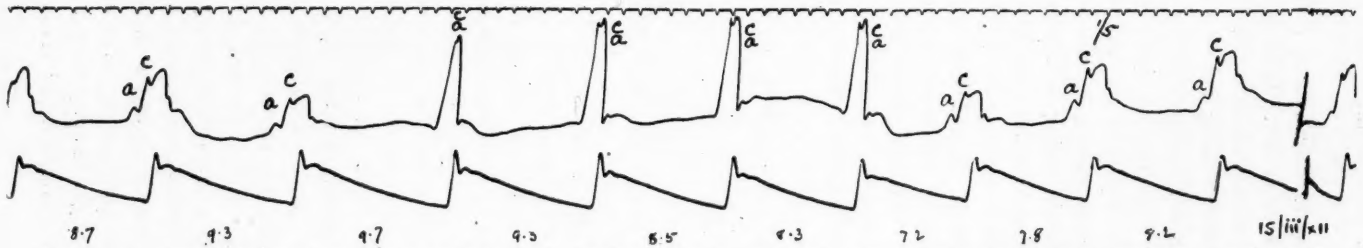


FIG. 4. A polygraphic curve from the same case as Fig. 1. The slow and slightly irregular sino-auricular rhythm is interrupted by four beats of nodal origin. The first nodal beat succeeds the longest pause in the curve. The nodal rhythm increases in rate as it proceeds.

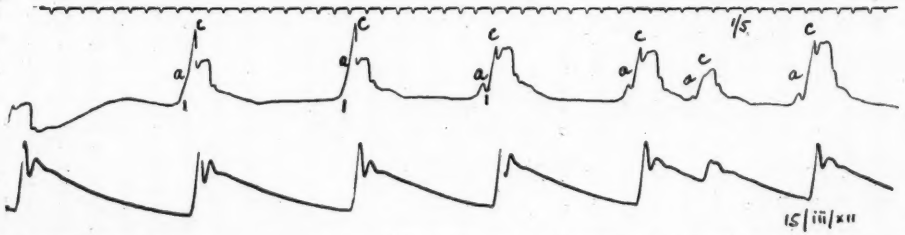


FIG. 5. A polygraphic curve from the same case as Fig. 1, showing two escaped contractions interrupting a slow and irregular sinus rhythm.

Thus we have evidence of two slow rhythms in the same case—rhythms of almost exactly the same rate; the one starting in the pacemaker, the other in the region of the *a.–v.* node.

Finally, we may examine another form of polygraphic curve, taken from the same patient and upon the same day. It is shown in Fig. 5. In the first two venous cycles the *a–c* intervals are reduced. This mechanism also follows as an indirect result of auricular slowing, but is much more fleeting than that already described. An electro-cardiogram showing the same phenomena is seen in Fig. 16. The first four beats of this figure are nodal and auricle and ventricle respond to common impulses; the last two ventricular contractions also coincide with auricular contractions, but these auricular contractions have a varying relation to the corresponding ventricular contractions and are of perfectly normal type in the electric curves; the auricular contractions come from the old pacemaker. The last summit R of Fig. 16 has an increased height because P is superimposed upon it. Similar events may be seen in Fig. 12. The first three cycles of this figure are nodal beats and auricle and ventricle both respond to the same impulses; the fifth and sixth also result from simultaneous contraction of auricle and ventricle, but the mechanism is different in these last cycles; P and R are superimposed. The largest R in this curve is that of the fifth cycle, in which the summits of R and P fall almost exactly together. In Fig. 13 three normal cycles are followed by two ventricular contractions with which normal auricular contractions coincide. The last R summit of this figure is the tallest. In the curves, in which there is this simple coincidence between auricular and ventricular contractions, the escape of the ventricle is also ascribed to a nodal impulse; the auricle does not participate because, being already in contraction, it is refractory.

The curious variation in the site of impulse-formation in this case permits me to refer again to distinctions which I drew between certain forms of impulse-formation in my book *The Mechanism of the Heart-beat*; for so far these distinctions have not been fully understood and appreciated. In speaking of new impulses as ectopic, I have restricted this term to an impulse formed in any portion of the heart other than the normal pacemaker or sino-auricular node. Now the abnormal beats in this case are of this nature, for they arise in all probability in the junctional tissues. To the extent of being ectopic the new impulses here described are similar to those which are encountered in cases of paroxysmal tachycardia. In this condition there is also a transference of the site of impulse-formation; and this transference from the position of the old pacemaker is also to the junctional tissues. But there is an essential distinction between the rhythmic beats of a paroxysm of tachycardia and the rhythmic beats of the new rhythm now described. The nodal rhythm which appears when impulses form too slowly at the sino-auricular node, or when this structure is destroyed experimentally, is the inherent or physiological rhythm of the structure in question; it might be aptly termed an *idio-nodal* rhythm. The impulses are formed at 35 or thereabout per minute and do not appear, when

the heart beats normally, because the old pacemaker is more active and consequently dominates the whole heart. Nevertheless, they are ready to appear so soon as the old rhythm is checked. To such a nodal rhythm I apply the adjective *homogenetic*, and class it under this term both with the old rhythm and with the idio-ventricular rhythm, for they all have the same quality. Homogenetic impulses, as I term them, are not defined according to site of origin. I use the term to distinguish such impulses from those which have the extra-systolic quality, namely, prematurity or rapidity of production; and these, in contradistinction to homogenetic, I call *heterogenetic*. The double classification, including site of formation and quality of impulse, clearly emphasizes the four distinct types of heart-beat.

1. The homogenetic type, arising in the old pacemaker; of which the normal heart-beats are the sole examples.

2. The homogenetic and ectopic type; of which the idio-ventricular and idio-nodal beats are characteristic examples.

3. The heterogenetic type, arising in the old pacemaker; of which the so-called sinus extra-systole is the sole example.

4. The heterogenetic and ectopic type; into which category all extra-systoles, other than those of sino-auricular origin, and all hitherto described paroxysms of tachycardia fall.

Case II. The second series of records which I propose to discuss at the present time were taken from a young man, who was sent to me by Dr. Mackenzie for electro-cardiographic examination. He was usually the subject of slow and generally irregular heart action. Through the kindness of Dr. Mackenzie I am in possession of the polygraphic curve. It is shown in Fig. 6. An irregular pulse curve is accompanied by a venous pulse tracing of the ventricular form; each arterial beat is accompanied by *c* and *v* waves. There is no pre-systolic wave *a*, though a curious wave (marked ?) occurs from time to time, the meaning of which is not clear; it is related to the preceding and not to the succeeding systole, but does not appear constantly. The electro-cardiograms are seen in Fig. 17. Fig. 17 (*I* and *II*) shows a regular ventricular beat of constant type and of the supraventricular form. There is no trace of auricular summit in any lead or during any part of diastole, neither are there any of those oscillations which are now known to characterize auricular fibrillation. So far as I am aware, no current interpretation is sufficient in explanation of these curves. Auricular fibrillation is excluded by the regular ventricular action present in these electro-cardiograms and in the left-hand portion of the polygraphic curve, and by the absence of oscillations; weakness of the auricular contraction [3] might explain the absence of *a* waves but would not explain the absence of P summits. Simultaneous auricular and ventricular contraction is improbable, though perhaps not definitely excluded, by the type of venous curve. The type of curve (electric and venous) was unchanged when irregularity occurred (Fig. 17, *III*).

[3] Venous stasis was not present.

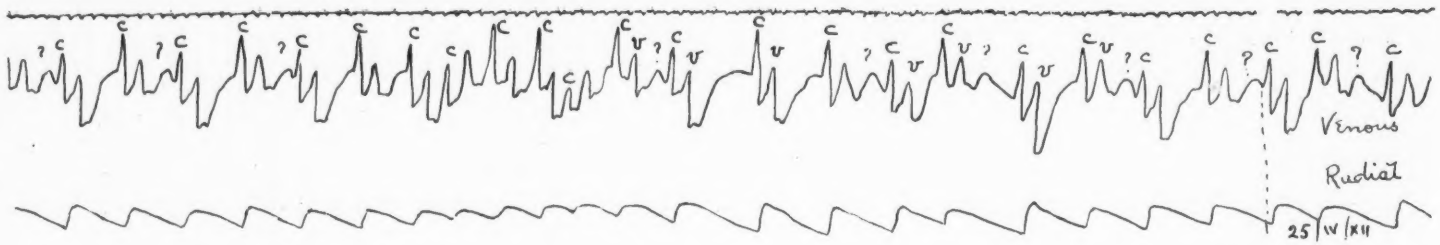


FIG. 6. A polygraphic curve, showing an irregular heart action, accompanied by the ventricular form of venous pulse.



FIGS. 7 and 8. Apex and radial curves. The radial pulse is regular, its rate being 24 per minute. The apex beats occur in twos and threes. The pauses in the radial curve are equal.

Case III. A farmer of 52 years was sent to me by Dr. Batten of the National Hospital in September, 1910, for an examination of the heart. He gave no history of previous illness. He complained of being easily fatigued and of having some shortness of breath on exertion. For three years he had suffered from fits in which consciousness was lost. On examination, increase of the cardiac dullness a half-inch to the left and a systolic apical murmur were discovered. The pulse was regular; the ventricle beat always in groups of two or three.

The polygraphic curves may be described first. Fig. 7 is from the radial artery and apex beat. The radial pulse is quite regular and the rate is about 34 per minute. The pulsations at the apex occur in groups of two and three beats; the first beat of each group corresponds to the radial pulsation, the remainder are not transmitted. Similar events are shown in Fig. 8. It is remarkable that, although the grouping of apex beats varies, the spacing of the groups is even. Fig. 9 is from the radial and jugular pulses. Each radial beat is found to be accompanied by perfectly clear *a* and *c* waves; a long pause follows and then there is a prominent wave. To what is this wave due? It occurs too far away from the commencement of systole (the distance is actually $\frac{3{\cdot}5}{5}$ sec.) to be a *v* wave. It falls at a time when the second beat of the ventricular group is in progress. This is clear from a comparison of Figs. 7, 8, and 9. It is still clearer in Fig. 10; here we have apex and venous curves side by side. It is not a *c'* wave, for it occurs later than the beginning of the second (by $\frac{1{\cdot}5}{5}$ sec.) and earlier than the beginning of the third systole of a group. Moreover, it is constant in position and is single, whether there are two or three ventricular beats in the group. It is a wave which is of much greater amplitude than the *c* wave which precedes it, yet it is accompanied by a weak ventricular systole. It is not the result of ventricular systole and must be attributed to an auricular systole, which coincides with a ventricular one. That the auricular contraction has no association with the third ventricular beat is shown by its accompanying groups of two beats (the last group of Fig. 10). It lies with a fair degree of constancy $\left(\frac{1{\cdot}5}{5}\text{ sec.}\right)$ after the second beat of the group; it is this relation which suggests that it is an auricular contraction which has been produced by a retrograde impulse, coming from the second ventricular contraction. If such is the true nature of the events, it may be asked why the pulse pauses are equal; the reply is that the second ventricular contraction of a group is retrograde while the third is not. It will be seen that there is no reason why this should not be the case; the first and second beats of a given group are further apart than the second and third. The interval for the retrograde impulse, the *Vs–As* interval of the second beat, is large; it amounts to $\frac{1{\cdot}5}{5}$ sec.; the failure of passage of a second impulse may therefore be the result of the relative prematurity of the third ventricular beat.

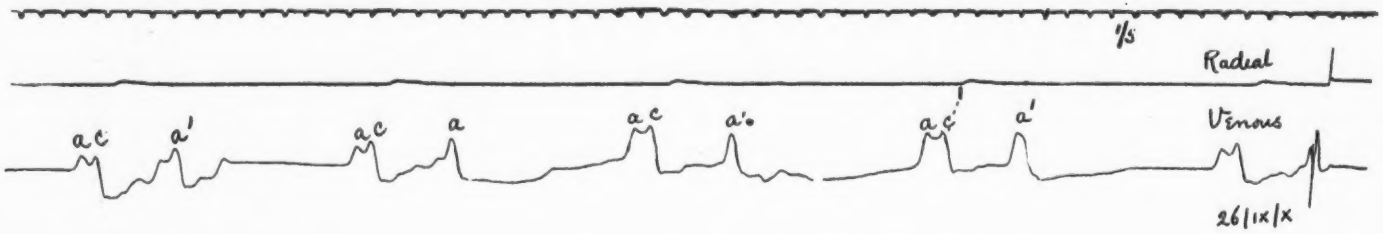


FIG. 9. A polygraphic curve from the same case as Fig. 7, showing venous and radial curves. The radial beats are accompanied by *a* and *c* waves from the jugular. During the pause a single wave *a'* appears. It is due to an auricular contraction.

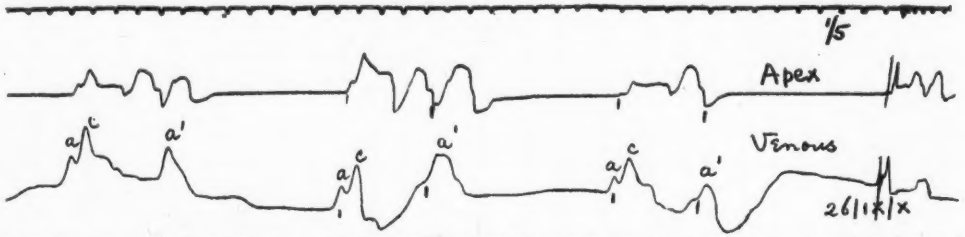


FIG. 10. Venous and apex curves from the same case, showing the relation of the wave *a'* to the grouped ventricular beats. The wave maintains its position whether there are two or three beats in the group.

The analysis which I have given may appear an uncertain one, because it is based on the interpretation of the curious additional waves in the venous curves. It is substantiated by the electro-cardiograms. These curves were taken on the preceding day; the rate of the pulse was then somewhat slower, being 26 per minute, but a similar mechanism was present. The ventricular beats occurred in couples or groups of three. An electro-cardiogram showing coupling is seen in Fig. 18. The first beat of each group is preceded by an auricular contraction P, and consists of the usual summits R, S and T. The first beat of each group is a perfectly normal heart cycle, in which the *As–Vs* interval (represented by the *F–R* interval) is 0·13 sec. The second ventricular beat of each cycle is anomalous in type. It is a premature contraction arising in the ventricle. Its outline is a familiar one, it corresponds very closely to the type of contraction obtained when the apex of the left ventricle is stimulated in the dog. But it differs from such beats and from similar beats which arise spontaneously in the human heart in one very essential respect. It will be seen to consist of a sharp downstroke, an upstroke, an almost horizontal portion and finally a slow rise and fall. But it is malformed at one point. The anticipated outline should follow the dotted line on the middle group of the curve. The curve is notched at the beginning of the slow rise. The notch is placed $\frac{3\cdot3}{5}$ sec. after the commencement of the first beat of the group and $\frac{1\cdot2}{5}$ sec. after the commencement of the second beat of the group. The relations of the curious waves in the venous curves (Fig. 9) to these points may be remembered: $\frac{3\cdot5}{5}$ sec. and $\frac{1\cdot5}{5}$ sec., a sufficient approximation, seeing that the curves were taken on different days and by different methods. The notched electro-cardiogram is the result of the same event as the venous wave in question; both are due to an auricular systole which falls with the second ventricular beat of a group. But its electric representative is directed downwards, while the usual auricular representative for this patient is an upwardly directed summit. The auricular contraction is an abnormal one; it has travelled in an abnormal manner through the auricle. Such an auricular electric complex is anticipated when the contraction commences below and travels upwards, as it would do were the auricular contraction propagated from the ventricle. The electro-cardiograms of the coupled periods consequently confirm the analysis of the venous curves.

A single consideration remains. If the first premature beat is retrograde and the second is not, then the electro-cardiograms of the groups of three beats should be of material assistance. The second and third beats of the group might be compared and it might be expected that they would differ only in regard to the notching, the second beat of the group being complicated by an abnormal auricular contraction, and the third beat of the group being free of it. The actual comparison however is not so easily accomplished, for the reason that in none of the curves are the second and third beats of a group identical. Some-

times they are totally different, and in all there is some divergence. Nevertheless the curves are sufficiently clear. Fig. 19 is an example. In the first group of this figure there are three ventricular cycles: the first is normal in every respect; the second is of the type seen in Fig. 5 and is distinctly notched; the third is of a new type, and the point at which the notch is expected is marked on the curve; no such notch occurs. The second group is a clearer example, for the two premature beats are alike in general form. The first of these premature beats (the second of the group) is notched, the second premature beat (the third of the group) is not distorted in the same fashion.

To sum up, the electro-cardiograms furnish corroborative evidence that the analysis of the venous curves, as it has been given, is correct, and that we are dealing with retrograde extra-systoles.

Conclusions.

Three cases of slow heart action of unusual form are described.

Case I. In a man who presented a continuous slow action of the whole heart, irregularity of the ventricle was observed. This was due in part to the building of homogenetic impulses at two centres and at almost equal rates. The centres of impulse-formation lay at the normal pacemaker and in the region of the *a.–v.* node.

Case II. Curves are described from a young subject who displayed slow and at times irregular heart action. The disorder, as illustrated by polygraphic and electro-cardiographic curves, was of a hitherto undescribed form. No trace of auricular contraction, either co-ordinate or inco-ordinate, could be discovered in any record, venous or electro-cardiographic.

Case III. A case in which the Adams-Stokes' symptom-complex was present is described. The pulse-rate was from 26 to 33 beats per minute. The ventricle beat in grouped fashion; the first beat of each group was of normal origin; the second beat of each group was premature and arose in the ventricle, it was also retrograde; the third beat, when it occurred, was premature and arose in the ventricle, but was not retrograde, and the pulse was consequently regular.

EXPLANATION OF FIGURES.

PLATE 14, FIG. 11. Electro-cardiograms from Case I, showing the three leads, *I*, right arm to left arm; *II*, right arm to left leg; and *III*, left arm to left leg. In leads *I* and *III* the heart is beating regularly at a rate of 54 per minute. In lead *II* the heart is beating irregularly, but the beats are of the same nature, being generated in the sino-auricular node. The horizontal lines in this and subsequent figures divide spaces equivalent to 10^{-4} volts. The time-marker is in $\frac{1}{30}$ seconds.

FIGS. 12–16. A series of curves from lead *II* from the same case; the lengths of the cycles are marked in thirtieths of seconds. Figs. 12 and 16 show three cycles in which auricle and ventricle respond to common and nodal impulses and two escaped contractions in which the ventricular beats are coincident with normal auricular contractions. Fig. 13. Three normal cycles are followed by two escaped contractions. Fig. 14 shows a single nodal beat followed by four normal cycles. Fig. 15 shows five nodal beats.

PLATE 15, FIG. 17. Electro-cardiograms from the three leads in Case II. In leads *I* and *II* the action of the heart is regular, the rate being 44 per minute. In lead *III* the heart action is irregular. In all the curves the mechanism is similar; the ventricular beats are of a supraventricular type and there is no sign either of a P summit or of the oscillations which characterize a fibrillating auricle.

FIG. 18. An electro-cardiogram from Case III (lead *II*), showing a bigeminal action of the ventricle. The first cycle of each couple consists of a normal sequential beat, the second beat of each couple is a premature beat, presumably arising from the left side of the heart. It differs from the beats known to originate in this neighbourhood in that it is notched. An inverted auricular complex follows with this anomalous ventricular complex and distorts it, as shown by the dotted line in the middle group of the figure. The figure illustrates retrograde heart-beats. The time-marker in this and Fig. 19 is in $\frac{1}{5}$ sec.

FIG. 19. An electro-cardiogram from the same case (lead *II*), showing the heart-beats grouped in threes. The first and second beats of each group are similar to those of Fig. 18. The third beat of each group is also of ventricular origin but comes from different points in the two instances. No trace of auricular contraction can be found to complicate this third beat. A comparison may be made between the two premature ventricular contractions in the right-hand group; the first of these is distorted by an inverted P, the second is not.

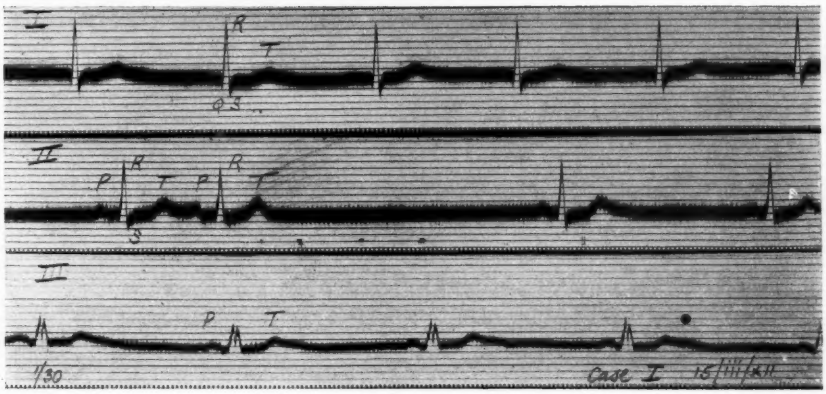


FIG. 11

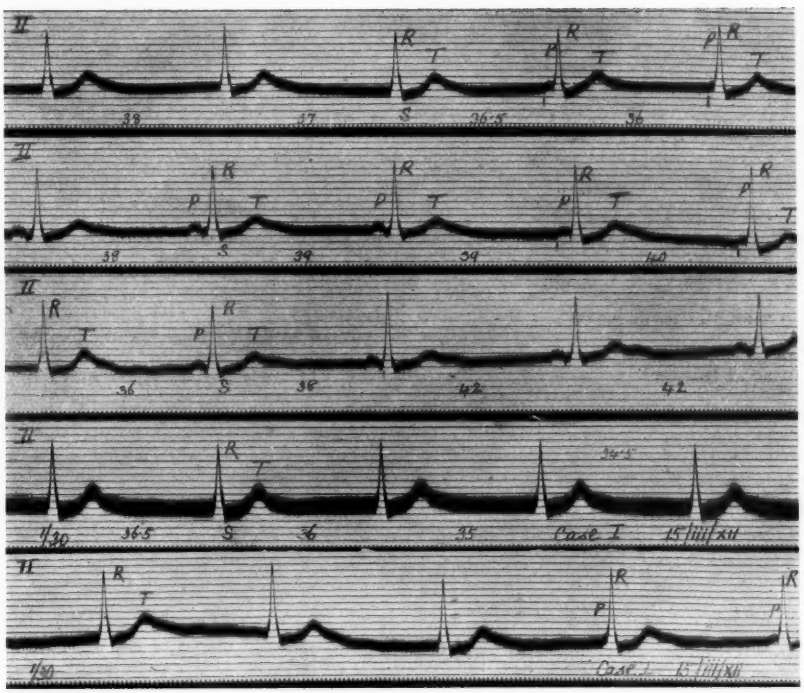


FIG. 12

FIG. 13

FIG. 14

FIG. 15

FIG. 16



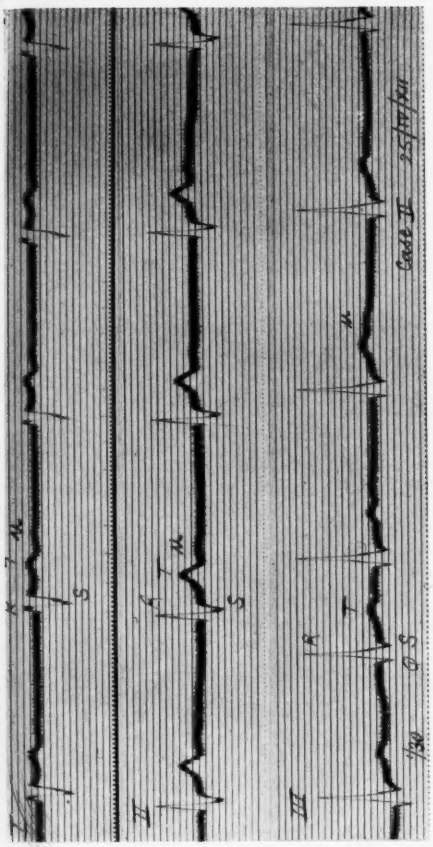


FIG. 17

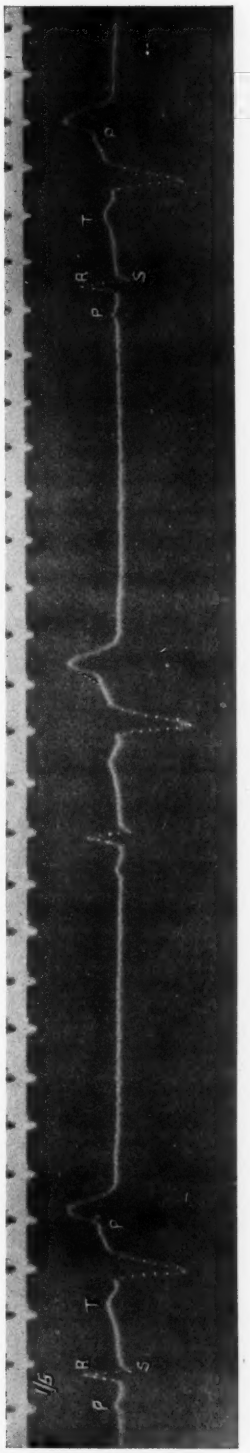


FIG. 18

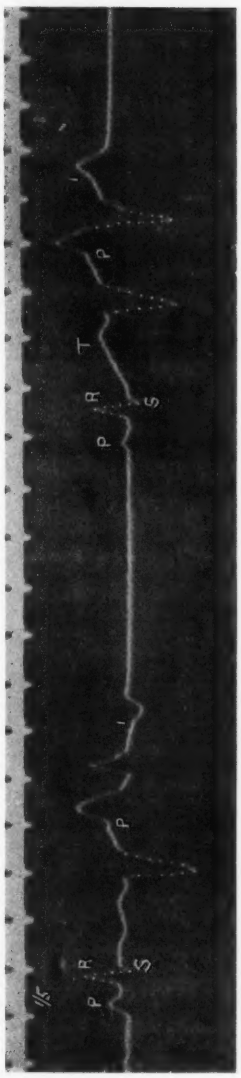


FIG. 19

A CASE IN WHICH A HIGH SPEED OF THE AURICLES DID NOT PRODUCE TACHYCARDIA

By WILLIAM E. HUME

THERE are certain instances on record in which a high speed in the auricles was not accompanied by a corresponding ventricular rate.

Gibson (1), Ritchie and Jolly (2), Goodhart and Hertz (3), Rihl (4), and more recently Lewis (5), have published polygraphic tracings in which there is shown a rapid auricular rate without a corresponding response from the ventricle.

In the present instance a similar case is published in which, however, the interpretation of the earliest jugular tracings was extremely difficult on account of their similarity to tracings exhibiting a normal *a. c. v.* sequence.

The patient, a labourer aged 63, was admitted to the Royal Victoria Infirmary, Newcastle-on-Tyne, on September 16, 1911.

History of illness. In May, 1911, the patient was troubled for the first time with shortness of breath on exertion. He continued to work as a labourer until June, 1911, when he had to give it up on account of dyspnoea and giddiness.

Previous health and habits. When 18 years of age he had some fever with pains in the back and the head, the nature of which is doubtful. Shortly after this illness the chest was crushed between two wagons. Eleven years ago he was in bed for three months on account of pain in both lumbar regions. Except for these illnesses he had been a healthy, hard-working labourer. He denied that he had suffered from rheumatism or venereal disease.

Condition on admission. On admission, September 16, 1911, the patient was able to lie in a recumbent position, and while at rest suffered little or no inconvenience.

On examination of the heart the apex was under the fifth rib, 5 inches from the middle line. The area of cardiac dullness extended from the fourth rib above, and was 0 and 5¼ inches from the mid-sternal line.

On auscultation at the apex there was a soft first sound with a systolic murmur, which was conducted towards the axilla, followed by a second sound.

The wall of the radial artery revealed no thickening, and the systolic blood-pressure was 150 mm. of mercury. On admission the pulse-rate varied between 90 and 101. The urine was normal and the lungs were clear. After admission to the hospital he was perfectly comfortable, and his stay was prolonged in order to study the varying rhythm of the heart which early manifested itself. He was discharged on January 18, 1912.

Numerous tracings were taken from the jugular veins, the radial artery, and the apex during his stay in the hospital. In order to follow the sequence of events the tracings will be described in chronological order.

On admission the rate of the radial pulse was 90 and the rhythm was for

the most part regular, though occasional pauses occurred. At the root of the neck it was noted that there was a very rapid, regular pulsation which appeared to be at least three times as rapid as the radial pulse.

To my surprise, however, I obtained Tracing No. 1 which did not appear to reveal the rapid pulsation which I could see in the neck.

Though the interpretation of Fig. 1 at first sight might seem to be explained by a normal *a. c. v.* rhythm, it will be seen that the down-stroke 6, indicating the end of the ventricular systole, occurs considerably before the apex of the apparent *v.* wave of the jugular tracing.

The interpretation of Fig. 1 is aided by a consideration of Fig. 2.

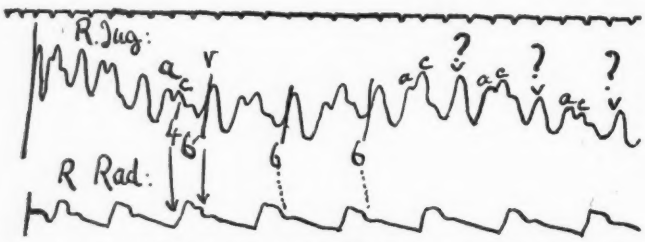


FIG. 1. Tracings of right jugular vein and radial artery. 4 = Radial upstroke; 6 = Opening of tricuspid valve and corresponds to the bottom of the radial dicrotic notch.

Here (Fig. 2) it will be seen that the radial artery is regular except at the places marked 1, 2, 3, and 4, where the diastolic periods are prolonged.

In the jugular tracing the numbered arrows point to the corresponding periods in the venous pulse.

If the Section 4, towards the right of the tracing, be analysed, two prominent waves a^1 and a^2 are found to occur during diastole. Similar waves occur in periods 1, 2, and 3. These waves seemed to correspond to the visible waves in the neck and were thought to be due to contractions of the auricle. As it was unlikely that such waves would be periodic or occasional, it was suggested that the auricular rate was constant and at the high speed represented by the isolated waves in periods 1, 2, 3, and 4.

On this assumption waves due to auricular contraction have been marked in Fig. 2, with the result that the auricular rate is found to be about 260 per minute. This interpretation is applied to Fig. 3 (and in reality also applies to Fig. 1) and a diagram is interposed.

In these three figures we obtain evidence of an auricular speed of about 260 per minute with a ventricular speed of about 87. There is for the most part a 3 : 1 heart-block. This interpretation was fully borne out by later occurrences and was the only explanation of three facts:

1. The visible presence of regular and rapid venous waves in the neck.

2. The frequent appearance of waves (such as a^1 and a^2 in Fig. 2) during diastolic pauses in the jugular tracings.

3. The abnormally late appearance of the *v* wave if an *a. c. v.* sequence (Tracing No. 1) were assumed.

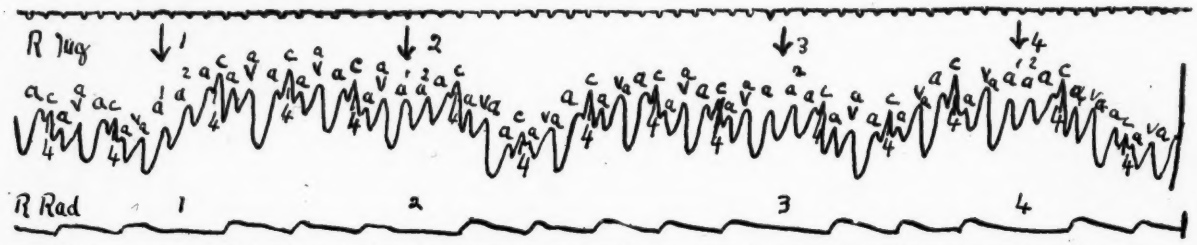


FIG. 2. Right jugular and radial tracings. Below the arrows waves a^1 and a^2 are seen, due to rapid auricular contractions which are marked (a) throughout the tracings. Auricular rate = about 260.

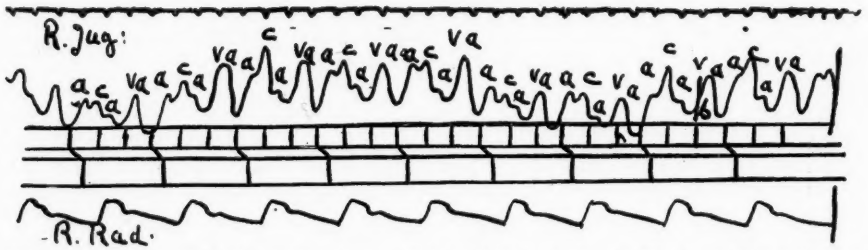


FIG. 3. Tracings from right jugular vein and right radial artery. This tracing is similar to Fig. 1, and the interposed diagram indicates the interpretation of Tracings Nos. 1, 2, and 3.

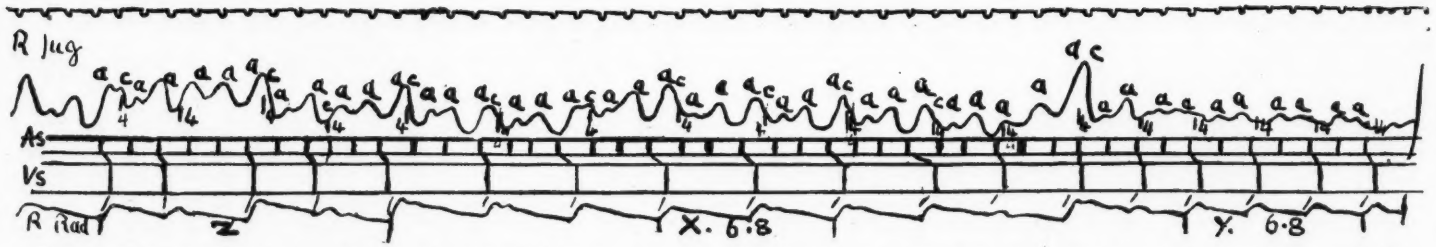


FIG. 4. Polygraphic curves from right jugular and radial pulses. Period Z shows alternating 2 : 1 and 3 : 1 heart-block. Period X shows 3 : 1 heart-block. Period Y shows 2 : 1 heart-block. The explanation of this figure is found in the text.

A week later, on September 22, the pulse was found to be very irregular and Fig. 4 was taken. The veins in the lower part of the neck still showed rapid regular waves. Three periods in the figure are marked *X*, *Y*, and *Z*.

The interposed diagram indicates the interpretation which is given of these periods *X*, *Y*, and *Z*. It was thought that the auricles were still in a condition of 'tachyauricle', and that the ventricles only responded to certain of the auricular impulses. It will be seen that the first period (marked *Z*) reveals alternating 3 : 1 and 2 : 1 heart-block. *X* and the three pulse periods immediately preceding it reveal a 3 : 1 heart-block. *Y* reveals a 2 : 1 heart-block.

In support of this view of the rhythm, it will be seen that *X*, containing two pulse periods, is equal to *Y*, which contains three pulse periods.

X and *Y* both equal 6·8 fifths of a second. In the jugular pulse (*a*) waves are placed where it is thought they appear.

This condition was only temporary, and alternated with the condition seen in Tracings 1, 2 and 3 until October 22, when the tincture of digitalis in 15 m. doses was administered every four hours. The administration of digitalis was stopped on October 28.

On October 27 the pulse-rate had fallen to 45 per minute and Tracing No. 5 reveals the condition at that time.

In Fig. 5 the jugular tracing shows rapid and regular waves at the rate of about 260 per minute. In the same period there are seven radial beats at the rate of 43 per minute. The radial beats are not quite regular. Similar waves due to auricular contraction can also be seen in tracings taken from the apex (Fig. 5).

On November 21 Fig. 7 was taken, and reveals definite fibrillation of the auricle. Since that date auricular fibrillation was constantly present.

On November 6, $\frac{1}{50}$ grain of atropin was injected. The diagram shows graphically the result of the experiment. Before the experiment the radial pulse showed the form and characteristics of Tracing No. 5 and the rate was 61–65, and the heart was still under the influence of digitalis.

Thirty minutes after the hypodermic injection of atropin the ventricular rate reached 106.

From this experiment it was concluded that the injection of atropin had released the effect of digitalis on the conductivity of the heart by removal of vagal inhibition, and that a larger number of auricular impulses reached the ventricle.

The ventricular rate was always easily controlled by the administration of digitalis both before and after the establishment of auricular fibrillation. On a second occasion (March, 1912) after the permanent establishment of auricular fibrillation, a second injection of atropin, $\frac{1}{50}$ grain, was administered, and the ventricular rate rose from 48–50 to 65–72 in twenty-five minutes. At no period did moderate exercise affect the rate of either auricles or ventricles.

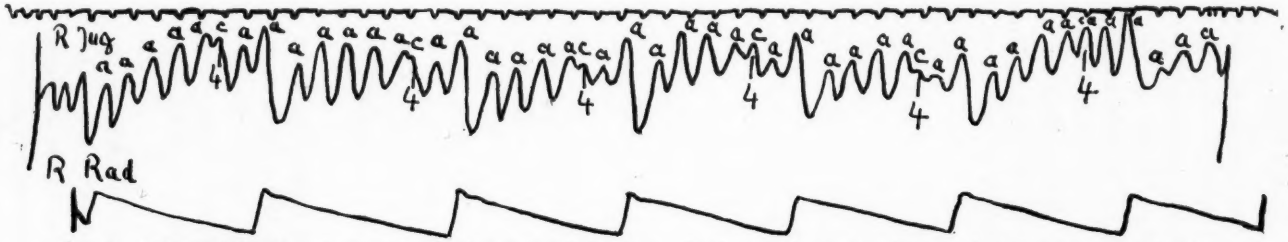


FIG. 5. Polygraphic curves from right jugular and radial pulses. In the jugular tracing large auricular waves are marked (*a*).

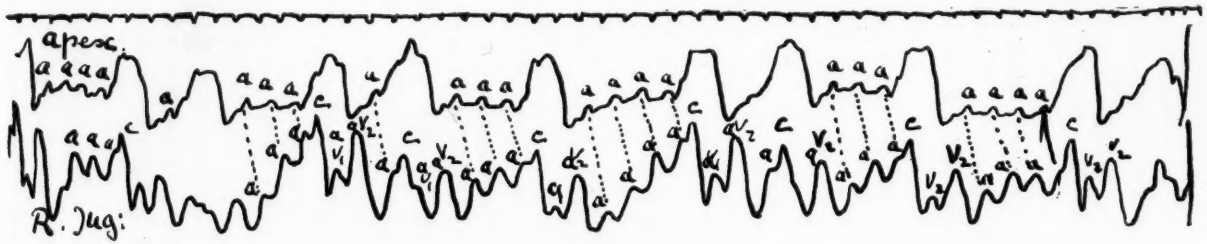


FIG. 6. Polygraphic curves from apex and right jugular vein. Definite waves (*a*) are seen in the apex tracing, which correspond to similar (*a*) waves in the jugular tracing.

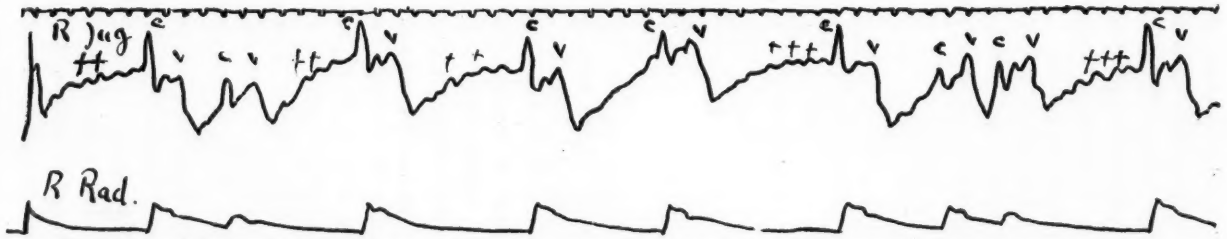


FIG. 7. Tracings from right jugular and radial pulses. The radial pulse is absolutely irregular, and small waves †† are seen in the jugular tracing.

The Relationship of the Present Case to certain other Published Cases.

This case seems to present certain features which bear resemblance to two groups of irregularity to which others have drawn attention:

(*a*) Cases in which a rapid action of the auricle is not accompanied by a corresponding tachycardia.

(*b*) The relationship between regular tachycardias of auricular origin and auricular fibrillation.

As regards the first group (*a*), Gibson, Ritchie and Jolly, Goodhart and Hertz, Rihl and Lewis have published cases in which there was present a rapid auricular rate without a corresponding response from the ventricle.

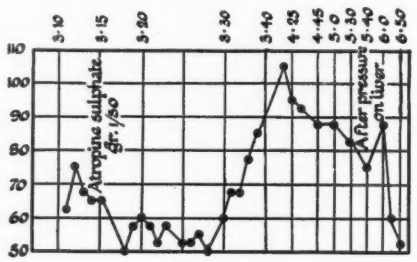


FIG. 8. Diagram illustrating atropin experiment. *Pulse-rates* indicated on left side of diagram. *Time* indicated on the top of the diagram.

In the first case (Gibson (1)) there was apparently complete heart-block, and fibrosis of the *a.–v.* bundle was discovered at the necropsy. The ventricular rate varied between 30 and 42, whilst the auricular rate in the published tracings was 168, though Ritchie states that it reached 350 at a later date.

In the second case (Ritchie and Jolly (2)) before the administration of atropin the auricular rate varied between 60 and 70, whilst the ventricles beat at a rate of 30–32. After the administration of atropin the auricular rate reached 273, and later as rapid a rate as 300.

The rate of the ventricles never exceeded 56. Three months later the auricular rate had reached 43. Eight months afterwards the auricles were found to be beating 300 to the minute. After six years I believe that the auricles are still beating rhythmically and at this excessive speed. The rhythm is uninfluenced by exercise, atropin, digitalis, or bilateral pressure on the vagi in the neck.

In the third case (Goodhart and Hertz) the rate of the auricles was almost constantly 234 and the ventricular rate varied between 72 and 120.

The last observers did not consider that there was any evidence of heart-block in their case, and that the discrepancy between auricular and ventricular rates was due to the physical inability of the ventricle to keep pace with the auricle.

Though the auricular rate was uninfluenced by atropin injections, the ventricular rate rose from 78 to 170 under its influence.

In relation to the onset of auricular fibrillation in the case now published, the first and third cases died while the auricles were beating rapidly and regularly. In the second case the condition is still present and the patient is able to earn a small livelihood. And a normal rhythm is said to be present in Lewis's case. In none did auricular fibrillation succeed the regular co-ordinate action of the auricles.

Though the first two cases showed definite clinical evidences of heart-block, Goodhart and Hertz, as mentioned above, did not consider that any impairment of the *a.-v.* bundle was present in their case. Unfortunately no autopsy was obtained. In the present case I think that there is in all probability some pathological interference with the conducting bundle.

As regards the second group (*b*), to which this case also bears similarity, Lewis and Schleiter (6) have shown in two cases the transition between the normal auriculo-ventricular sequence and auricular fibrillation through three stages:

1. Single premature auricular contractions from a heterogenetic focus.

2. Tachycardias of auricular origin from a single heterogenetic focus in the auricle.

3. A stage in which multiple foci are active in the production of auricular fibrillation.

The chronological history of the present case as shown in the series of tracings bears out the thesis contained in Lewis and Schleiter's paper, and the subject so thoroughly discussed by them need not be further elaborated in this place.

BIBLIOGRAPHY.

1. Gibson, *Brit. Med. Journ.*, 1906, ii. 23.
2. Jolly and Ritchie, *Heart*, Lond., 1910–11, ii. 177.
3. Hertz and Goodhart, *Quart. Journ. Med.*, Oxford, 1908–9, ii. 213.
4. Rihl, *Zeitschr. f. exper. Pathol. u. Therap.*, Berlin, 1911, ix. 277.
5. Lewis, *Heart*, Lond., 1911–12, iii. 285.
6. Lewis and Schleiter, H. G., *Heart*, Lond., 1911–12, iii. 173.

CONGENITAL FAMILY STEATORRHOEA

By A. E. GARROD and W. H. HURTLEY

(From the Hospital for Sick Children, Great Ormond Street, and the Chemical Laboratory, St. Bartholomew's Hospital)

The term stearrhoea, or steatorrhoea, has had an unfortunate history. It was originally employed, by Kunzmann (1) in 1824, to designate the passage of liquid fat with the stools, but was applied later, by Erasmus Wilson, to the disease of the skin commonly known as seborrhoea. This latter use of the word seems to have been almost wholly abandoned by dermatologists, but is placed first in medical dictionaries, whereas its original significance, in which it cannot be spared, is relegated to the second place.

To add to the confusion, some modern writers apply the name steatorrhoea to the passage of fatty stools of all kinds, instead of limiting its use to the special phenomenon which Kunzmann observed in the cases which he investigated and which Richard Bright (2), writing in the year 1832, described in the following ponderous sentence: 'The symptom to which I refer is a peculiar condition of the alvine excretion, a portion more or less considerable assuming the character of an oily substance resembling fat, which either passes separately from the bowels, or soon divides itself off from the general mass, and lies upon the surface, sometimes forming a thick crust, particularly about the edges of the vessel, if the faeces are of a semi-fluid consistence, sometimes floating like globules of tallow which have melted and become cold.' It is in this special sense that the term steatorrhoea is employed in the present paper, as an equivalent of the German term 'Butterstühle'.

Such steatorrhoea had been described long before Kunzmann wrote, amongst others by Tulpius (3) in the seventeenth century, but it was he who suggested its intimate connexion with the disease of the pancreas present in his case. Bright also, who was apparently unacquainted with Kunzmann's writings on the subject, argued in favour of such a connexion, in his paper from which we have quoted, although the presence of malignant ulceration of the duodenum in his cases raised a doubt whether the pancreas was alone responsible.

Increased knowledge and the multiplication of observations have served to emphasize this association, and in a recent article H. Saloman (4) goes so far as to state that the excretion of butter-like fat with the stools indicates with certainty deficiency of pancreatic secretion. On the other hand, the cases of pancreatic disease in which steatorrhoea is observed in its more pronounced form

are comparatively few. Nor are clinical experience and physiological observation at variance in this matter. It is known that the pancreatic steapsin plays the chief part in the splitting of fats in the alimentary canal, and true steatorrhoea is closely connected with the abundant presence of unsplit fat in the stools. Yet, although not a few observations bear witness to the importance of an undue proportion of unsplit to split fat in the stools as an evidence of pancreatic disease, in other cases, although the amount of fat in the stools has been very large, the ratio of neutral fat to fatty acids and soaps has been within the normal limits.

Stools rich in fat are met with in association with other morbid conditions, such as diseases of the intestinal walls, lardaceous or ulcerative, and occlusion of the bile duct, but clinical experience does not associate true steatorrhoea with such conditions.

That steatorrhoea of pancreatic origin may persist for years without any serious detriment to health is proved by a case recorded by T. J. Walker (5) of a medical man who first exhibited this symptom at the age of 62, but who continued to live an active and vigorous life. After his death, at the age of ninety years, his pancreas was found to be almost wholly replaced by fat; calculi were present, and had completely blocked the duct, which was greatly dilated.

Cases of temporary steatorrhoea are on record, but in most of these the clinical data are too incomplete to allow any conclusions to be drawn as to the presence or absence of pancreatic disease. However, Finizio (6) has recently described the occurrence of a transient steatorrhoea in a child, in association with the pancreatitis of mumps.

An interesting case of steatorrhoea in a child is mentioned by Sir Everard Home (7), in a paper published in 1813.

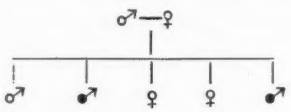
A little girl, Elizabeth Ryder, four years of age, had been healthy for six months after birth, but afterwards lost flesh, acquired a sallow complexion, and was liable to jaundice. At eighteen months her belly became tumid, and she showed weakness of the back and limbs. When she was three years old 'her mother observed something coming from her as she walked across the room, which, when examined, was found to be fat in a liquid state, which concreted when cold'. From that time onward she voided, at intervals of ten to fourteen days, some three ounces of fat, sometimes pure, and sometimes mixed with faecal material. The subsequent history of this child is not recorded, but it is obvious that, in view of the abdominal symptoms, a lesion of the pancreas cannot be excluded.

We have found no record of cases such as that to be described, in which the steatorrhoea was congenital, and unattended by any signs of illness.

Clinical Features.

Harry C., aged 6 years, was admitted to the Hospital for Sick Children, under the care of one of us, on January 4, 1911. He was brought to the Hospital by his mother because he 'passed grease' from the bowel.

The boy is the second of a family of five children, of whom only two survive. The eldest died of bronchitis at the age of seven months; the third at six weeks with convulsions; and the fifth at eleven months of measles and broncho-pneumonia. The parents, who are healthy, are *first cousins*.



His mother, who is an excellent witness, states that she was prevented by illness from attending to the child during the first seven months of his life, but that, as soon as she took charge of him, she noticed the peculiarity of his motions, which has persisted ever since. Her youngest child, also a boy, who died at the age of eleven months, exhibited a like peculiarity from birth, and there can be little doubt that he was the subject of the same anomaly. She is sure that the three other children were not similarly affected, and no other case than these two is known to have occurred in the family of either parent. The boy Harry was a small baby, but healthy, developed naturally, and walked at twenty months. At the age of three years he was an inmate of the German Hospital for some months, under the care of Dr. Karl Fürth, who has kindly furnished us with some information as to his condition at that time, which will be referred to later. Suffice it to say here, that then, as now, he exhibited steatorrhoea.

When admitted to the Hospital for Sick Children he appeared to be in excellent health and spirits, and, save for the conditions of his motions, exhibited no signs of disease. At six years and eleven months his development was little below the average for his age. He showed no signs of infantilism, and was bright and intelligent. Nothing in his appearance suggested that he had ever been the subject of rickets.

	H. C., aged 6 years 11 months.	Galton's average for a boy of 6 years 11 months.
Height	44 inches	45 inches
Weight in clothes	44 pounds	48 pounds

According to the same statistics the height of H. C. was that of an average boy of 6 years and 8 months, and his weight that of a boy of 6 years and 4 months.

His appetite had always been large, and he compensated instinctively for the waste of fats by an excessive intake of carbohydrates. When allowed to take as much bread as he wished he consumed 24 oz. or more in the day.

Careful examination failed to reveal any evidence of visceral disease, and his urine contained neither albumin nor sugar.[1]

[1] A specimen of urine, passed on Feb. 12, 1911, reduced Fehling's solution, showed a dextro-rotation corresponding to 0·5 per cent dextrose, and yielded an osazone which melted at 201° C. The next specimen passed contained no sugar. There was a diabetic patient in the ward, but the specimen was certainly not his, and no possibility of error could be traced; no sugar was found at any previous or subsequent examinations, even when 100 grammes of glucose were added to a diet rich in carbohydrates. The fact has to be recorded, but we are not disposed to lay any great stress upon it.

His stools presented the appearance characteristic of true steatorrhoea. When a diet rich in fat was taken they contained large quantities of liquid fat, which solidified on cooling, to form a plate around the faecal mass. Liquid fat escaped involuntarily from the anus at times, and, especially in hot weather, the decomposition of the fat so passed gave rise to a peculiar rancid and highly offensive odour, which clung about the patient, and was one of the chief causes of complaint.

On microscopical examination of the stools many fat globules and crystals of fatty acids were seen, but no starch granules or undigested muscle fibres. Dr. J. G. Forbes, who made a bacteriological examination of a stool, reported that film preparations showed a conspicuous predominance of gramme-negative over gramme-positive organisms. Dilutions were made from broth inoculations, and subcultures were planted upon agar plates, plates of Conradi-Drigalsky medium, and of bile-salt agar. The resulting growths were shown, by subculture tests, to belong entirely to the *B. coli* group of organisms, and a number of colonies which were tested individually yielded the characteristic reactions of *B. coli communis*.

The stools had the peculiar offensive odour referred to above, were pale and unformed, and on some occasions were so bulky as to be fitly described by the epithet elephantine.

It is obvious that the boy has no occlusion of the common bile duct. The absence of jaundice and the presence of pigment in the stools suffice to exclude this. However, it was desirable to exclude the absence of bile salts as a selective defect of biliary secretion. Accordingly, whilst the patient was taking a diet free from ostensible fat, and when his stools were, in consequence, normal in appearance, a specimen of faeces was examined for cholalic acid by the method recommended for the detection of the normal traces of that substance. The extract yielded a rather more intense Pettenkofer's reaction than that of the stool of a boy of like age which was examined as a control. Again, to exclude a disturbance of sulphur metabolism, with which might be associated a defective formation of taurocholic acid, Dr. T. S. Hele made some determinations of the sulphur excretion in the urine. His figures fall within the limits of normality. The averages of four days were as follows:

Total sulphur.	Sulphate.	Neutral sulphur.	% Sulphate.	% Neutral sulphur.
1·110	0·959	0·151	86·075	13·925

all calculated as SO_3.

Save the imperfect absorption of fats, there are in the case of H. C. no symptoms indicative of an intestinal disorder, and the fact that the motions are habitually unformed is sufficiently accounted for by their richness in fat. Examination of the abdomen revealed nothing abnormal, and when a diet almost free from fat was taken, the boy's stools became natural in appearance, both as to colour and consistence.

The exclusion of disease of the pancreas, which was so strongly indicated by the character of the stools, is naturally a matter of far greater difficulty; but the existence of such disease appears highly improbable in view of the evidence that the anomaly has been present from birth, and the general well-being of the boy. Moreover, such tests of pancreas efficiency as were applied lend no support to such a theory of the origin of the steatorrhoea.

A formalized gelatin capsule, containing methylene blue, was swallowed at *1.30 p.m.* The urine passed at 6 p.m. was not tinted, but the pigment was present in a specimen passed at 4 a.m. the next morning.

Schmidt's silk bag test was applied. The minute silk bags, containing cubes of beef hardened in alcohol, were swallowed at 10 a.m. and were passed at noon on the following day. Control bags, taken at the same time by a child with chorea, were passed at 6 p.m. on the following day. Dr. Forbes reported upon

both sets as follows: 'Sections of the beef cubes, enclosed in silk, both from H. C. and the control child, showed undigested muscle, retaining the nuclei in the central portions; but in the peripheral parts there was evidence of digestion and loss of nuclei in the case of H. C., but without loss of nuclei in the control.'

Dr. Cammidge, who was kind enough to examine the faeces and urine, reported a very slightly positive result of his own pancreatic test. Heiberg's test, applied to the faeces, gave a satisfactory digestion of casein, and the results of these and other examinations made by him led him to the conclusion that the boy had no such serious disease of the pancreas as the characters of the stools would suggest.

Microscopic examination of the stools after a meal of beefsteak showed an absence of undigested muscle fibres, and the nitrogen of the faeces was not above the normal average for the diet taken. Lastly, Loewi's (8) ocular test was tried. The installation into the conjunctival sac of a few drops of a 1 in 1000 solution of adrenalin produced no dilatation of the pupil.

These results indicate that there is no defect of the pancreatic *secretion* as a whole, for tryptic digestion is apparently unimpaired. The high degree of tolerance of carbohydrate affords evidence of activity of the internal secretion of the gland, and its influence upon fat assimilation is alone open to suspicion.

It seems probable that our patient is the subject of an inborn error, hitherto undescribed, and on a par with such anomalies as alkaptonuria and cystinuria. Such an explanation gains in probability from the congenital character of the anomaly, and the fact that, although inconvenient, it is apparently little harmful. The family tree closely resembles that of an alkaptonuric family, well known to us (9), in which two out of five children of a first-cousin marriage are affected, and this resemblance suggests that, like alkaptonuria, this congenital familial steatorrhoea is a Mendelian recessive characteristic.

Such rare recessive characteristics will be especially apt to manifest themselves in the children of parents who are closely related; for intermarriage of stocks in which they are transmitted will afford the best opportunities for the union of recessive gametes, and the appearance of recessive qualities which may have been dormant for generations.

It may be hoped that, now that attention has been directed to the anomaly under discussion, other examples of it may be observed and placed on record from time to time.

It is probable that the subject of alkaptonuria or cystinuria lacks an enzyme to which is entrusted a particular metabolic task, which in consequence fails to be carried out; and one is tempted to suppose that in congenital steatorrhoea some agent which facilitates absorption is, in like manner, wanting. Accordingly, in the hope of throwing light upon the nature of the defect, a large number of estimations of the fats, fatty acids, and soaps in the faeces were carried out.[2]

[2] I desire to state that all the analyses embodied in this paper were made by Dr. Hurtley. —A. E. G.

The Diet of the Patient.

In the tables which follow three diets are referred to as Diets A, B, and C respectively.

Diet A was that taken over considerable periods covered by analyses. As it was proposed to put the boy upon a constant weighed diet, he was allowed to have what quantities of food he liked during several successive days, and in this way a standard was arrived at in accordance with his tastes and needs. The amount of fat contained in each individual constituent was determined, and the results are given in the following table:

		% Fat.	Fat per diem.
Milk	1·5 pint = 852 c.c.	3·17	27·01 grm.
Bread	24 oz. = 680·4 grm.	1·27	8·64 ,,
Mince	·5 oz. = 141·7 ,,	11·59	16·43 ,,
Dripping	3 oz. = 85·0 ,,	99·68	84·73 ,,
Butter	1 oz. = 28·4 ,,	84·28	23·94 ,,
Bacon	1 oz. = 28·4 ,,	46·11	13·10 ,,
Pudding	5 oz. = 141·7 ,,	2·41	3·42 ,,
		Total fat	177·27

The noticeable feature of Diet A, apart from its richness in fat, which was deliberately arranged, is the very large quantity of bread consumed in the day. This represents the boy's instinctive compensation for the loss of fat.

Diet B was the same as Diet A, except that the 3 oz. of dripping were replaced by 3 oz. of jam. The total fat in this diet was about half of that contained in Diet A, viz. 92 grm. per diem. The amount approximates to that contained in A. Schmidt's test diet.

Diet C was ostensibly free from fat, and consisted of lean meat, fish, biscuits, fruit, lemonade, and soda water. The amount of fat in this diet was not determined.

On February 19, 23, and 27, 1911, 30 oz. of bread were taken, whereas after these dates the quantity was reduced to 24 oz. This difference has been allowed for in the tables.

Method of Analysis.

The stool was well mixed after being weighed. For the analysis 30 or 40 grm. were taken. This quantity was dried by adding absolute alcohol and evaporating with frequent stirring on a boiling water-bath. It was then placed in a desiccator containing strong sulphuric acid. The dried specimen was transferred without loss to the extraction apparatus, and extracted continuously for forty-eight hours, as trials showed that only insignificant quantities could be extracted after this time. The thimbles employed were weighed after standing many hours in the balance-case to obtain a constant weight. The ether employed had been allowed to stand over solid caustic potash and potassium

permanganate for many days; it had then been re-distilled. It was not coloured by rosaniline acetate after this treatment, thus showing that it contained neither water nor alcohol. After the extraction, the ether was distilled off on a water-bath and the flask placed in a steam oven for one hour. It was then weighed. The thimbles were allowed to stand in the air until the smell of ether had disappeared, and before weighing were kept many hours in the balance-case to obtain constant weight. The sum of the extract and dry residue is the total dry faeces corresponding to the quantity of moist faeces taken for analysis. From this the day's *Total Dry Faeces* was calculated. The whole of the ether extract was dissolved in absolute alcohol and titrated with standard caustic soda, phenol-phthalein being the indicator. The amount of alcohol was very large in comparison with the amount of caustic soda employed. To obtain the soap the residue from the thimble was transferred to a porcelain dish, thoroughly ground with dilute hydrochloric acid, tested to see that it was strongly acid, and evaporated to dryness on the boiling water-bath. The perfectly dried residue was transferred at once to the thimble from whence it came and extracted continuously for twenty-four hours. The ether was distilled off, the flask was placed in the oven as before and weighed. The residue was titrated under the same conditions as before. The weighing and the figure from the titration agreed surprisingly well in most cases. That resulting from the titration is always employed in the tables given. The fatty acids obtained in both extractions are expressed as stearic acid. No attempt has been made to estimate the lipoid substances extracted with the fat. In the tables, therefore, the expression 'total fat excreted' is to be taken as meaning the sum of:

(*a*) Neutral, or unsplit fat together with lipoids.

(*b*) Fatty acids calculated on the assumption that the acid is all stearic.

(*c*) Soaps calculated on the assumption that all the acid combined as soap is stearic acid.

Table I. Table of Averages.

	Totals.					Percentages.					Utilization.		
	Dry Faeces.	Fat excreted.	Neutral Fat.	Fatty Acids as Stearic Acid.	Soap as Stearic Acid.	Fat in Dry Faeces.	Neutral Fat in Total Fat.	Fatty Acid in Total Fat.	Soap in Total Fat.	Total Split Fat in Total Fat.	Fat excreted per 100 of Fat taken.	Fat absorbed per 100 of Fat taken.	Total Non-fatty Residue.
Control Boy—													
Diet A, last 3 days . . .	10·0	1·4	0·7	0·3	0·3	14·5	52·1	24·0	23·9	47·9	0·8	99·2	8·6
Patient H. C.—													
Diet C, April 20,* 1 day .	10·4	4·6	2·5	1·6	0·5	44·0	54·7	35·2	10·0	45·2	–	—	5·8
Diet B, Oct. 24–27, 4 days	42·9	23·8	7·8	10·9	5·0	55·5	32·0	45·5	22·5	68·0	25·9	74·1	19·1
Diet A, 9 days	53·5	42·6	25·6	14·0	2·9	79·4	61·4	32·6	6·0	38·6	24·0	76·0	10·9
Diet A + Fel Bov. (green), May 14–18, 5 days . .	65·2	54·5	21·0	28·9	4·6	83·4	39·8	52·0	8·2	60·1	30·8	69·2	10·7
Diet A + Fel Bov. (brown), Oct. 16–21, 6 days . .	55·0	42·2	27·5	12·2	2·5	77·1	65·8	28·6	5·6	34·2	23·8	76·2	12·8
Diet A + Glycocholate, Oct. 8–11, 4 days . . .	61·8	50·7	33·5	14·9	2·3	82·2	63·4	31·4	5·2	36·6	28·7	71·3	11·1
Diet A + Pankreon 5th day, 1 day	90·6	79·3	35·0	43·8	0·5	87·5	44·1	55·3	0·6	55·9	44·8	55·2	11·3
Diet A + Holadin 3rd day, 1 day	115·9	95·6	30·5	55·3	9·8	83·0	31·9	57·8	10·3	68·1	54·0	46·0	20·3

* The sixth day on Diet C.

In calculating the averages the first day of any given diet has been omitted, and two stools passed on the same day have been reckoned as the stool of one day.

For constitution of Diets A, B, C see p. 247.

TABLE II. DETAILED TABLE.

Patient H. C. 1911. *Diet.*	Date.	Totals. Dry Faeces.	Fat excreted.	Neutral Fat.	Fatty Acids as Stearic Acid.	Soap as Stearic Acid.	Percentages. Fat in Dry Faeces.	Neutral Fat in Total Fat.	Fatty Acid in Total Fat.	Soap in Total Fat.	Total Split Fat in Total Fat.	Utilization. Fat excreted per 100 of Fat taken.	Fat absorbed per 100 of Fat taken.
Diet A	Feb. 19	72·58	53·1	39·1	12·7	1·31	73·0	73·6	23·9	2·5	26·4	29·7	70·3
Diet A + Fel Bov.	,, 23	34·19	28·5	23·7	3·5	1·31	83·0	83·2	12·3	4·5	16·8	15·9	84·1
,, ,, ,,	,, 27	14·84	11·5	7·6	3·3	0·61	77·0	66·1	28·6	5·3	33·9	6·4	93·6
More varied diet	Mar. 7	98·52	78·15	13·94	53·45	10·76	79·0	17·8	68·4	13·8	82·2	43·7	56·3
Diet A	April 4	44·47	37·86	14·53	19·79	3·45	85·0	38·4	52·3	9·3	61·6	21·4	78·6
Diet A + Pankreon	,, 9	90·63	79·3	34·98	43·82	0·53	87·5	44·1	55·3	0·6	55·9	44·8	52·2
,, ,,	,, 12	76·89	68·9	22·86	34·89	7·16	84·0	35·2	53·8	11·0	64·8	36·7	63·3
Diet A	,, 14	89·39	74·1	32·10	30·83	11·03	83·0	43·3	41·6	15·1	56·7	41·9	58·1
Diet C	,, 20	10·40	4·6	2·52	1·62	0·45	44·0	54·8	35·2	10·0	45·2	—	—
Diet A + Holadin	May 9	37·42	29·96	18·23	9·54	2·19	80·0	60·8	31·8	7·4	39·2	16·9	83·1
,, ,,	,, 11	115·94	95·64	30·48	55·33	9·83	83·0	31·9	57·8	10·3	68·1	54·0	46·0
Diet A + Fel Bov.	,, 14	81·77	66·11	14·11	42·55	9·45	81·0	21·3	64·4	14·3	78·7	37·3	62·7
,, ,, ,,	,, 15	36·22	30·17	18·15	10·60	1·42	83·0	60·2	35·1	4·7	39·8	17·0	83·0
,, ,, ,,	,, 16	71·12	57·98	28·64	25·60	3·74	81·5	49·4	44·1	6·5	50·6	32·8	67·2
,, ,, ,,	,, 17	82·41	72·17	35·23	33·61	3·33	87·5	48·8	46·6	4·6	51·2	40·8	59·2
,, ,, ,,	,, 18	54·43	45·90	8·87	31·96	5·07	84·0	19·3	69·6	11·1	80·1	25·9	74·1
Diet A	Oct. 5	34·18	25·77	19·35	5·66	0·76	75·4	75·1	22·0	2·9	24·9	14·6	85·4
,,	,, 6	29·46	24·57	18·82	5·26	0·49	83·4	76·6	21·4	2·0	23·4	13·9	86·1
Diet A + Glycocholate	,, 7	54·64	44·16	?	?	2·73	80·8	?	?	6·2	?	24·9	75·1
,, ,,	,, 8	45·61	37·11	16·66	16·80	3·65	81·4	44·9	45·3	9·8	55·1	21·0	79·0
,, ,,	,, 9	82·10	65·09	50·78	12·43	1·88	79·3	78·0	19·1	2·9	22·0	36·8	63·2
,, ,,	,, 10	69·99	59·54	41·10	16·84	1·60	85·1	69·0	28·3	2·7	31·0	33·6	66·4
,, ,,	,, 11	49·67	41·21	25·44	13·61	2·16	83·0	61·7	33·0	5·2	38·2	23·3	76·7

April 20. Diet C had been started on April 16.

May 11. Diet A was started on May 6 and Holadin on the same day.

May 14. No stool on May 12 and 13, therefore this is the stool of three days.

TABLE II. DETAILED TABLE (*continued*).

Patient H. C. 1911. *Diet.*	Date.	Totals. Dry Faeces.	Fat excreted.	Neutral Fat.	Fatty Acids as Stearic Acid.	Soap as Stearic Acid.	Percentages. Fat in Dry Faeces.	Neutral Fat in Total Fat.	Fatty Acid in Total Fat.	Soap in Total Fat.	Total Split Fat in Total Fat.	Utilization. Fat excreted per 100 of Fat taken.	Fat absorbed per 100 of Fat taken.
Diet A	Oct. 12	36·70	28·10	17·53	9·52	1·05	76·6	62·4	33·9	3·7	37·6	15·9	84·1
,,	,, 13	56·26	44·76	30·30	12·62	1·84	79·6	67·7	28·2	4·1	32·3	25·3	74·7
,,	,, 14	79·39	64·96	44·86	16·20	3·90	81·8	69·1	24·9	6·0	30·9	36·7	63·3
,,	,, 15	39·00	29·83	13·72	13·60	2·51	76·5	46·0	45·6	8·4	54·0	16·9	83·1
Diet A + Fel Bov.	,, 16	57·22	46·15	28·16	14·00	3·99	80·7	61·0	30·3	8·6	38·9	26·1	73·9
,, ,, ,,	,, 17	20·93	15·54	10·08	4·79	0·67	74·3	64·9	30·8	4·3	35·1	8·8	91·2
,, ,, ,,	,, 18	62·34	50·37	30·48	17·64	2·25	80·8	60·5	35·0	4·4	39·4	28·5	71·5
,, ,, ,,	,, 19	75·37	48·55	30·54	14·72	3·29	64·3	62·9	30·3	6·8	37·1	27·4	72·6
,, ,, ,,	,, 20	40·02	33·17	26·12	5·84	1·20	82·9	78·7	17·6	3·6	21·2	18·7	81·3
,, ,, ,,	21	11·04	9·85	6·53	1·77	1·55	89·2	66·3	18·0	15·7	33·7	33·5	66·5
,,	21	63·34	49·48	33·15	14·53	1·80	78·1	67·0	29·4	3·6	34·0		
Diet B	,, 22	41·28	33·61	20·53	11·01	2·07	81·4	61·1	32·8	6·1	38·9	19·0	81·0
,,	,, 23	—	—	—	—	—	—	—	—	—	—	—	—
,,	24	32·22	16·77	6·36	6·98	3·43	52·1	37·9	41·6	20·4	62·0	30·8	69·2
,,	24	21·89	11·49	3·20	6·70	1·59	48·4	27·9	58·3	13·8	72·1		
,,	,, 25	31·84	16·11	4·98	6·09	5·04	50·6	30·9	37·8	31·3	69·1	17·5	82·5
,,	,, 26	31·41	18·86	4·92	9·56	4·38	60·0	26·1	50·7	23·2	73·9	20·5	79·5
,,	27	43·46	25·92	9·66	11·85	4·41	59·6	37·3	45·7	17·0	62·7	34·8	65·2
,,	,, 27	10·70	6·02	2·25	2·58	1·19	56·3	37·3	42·9	19·8	62·7		
Control Boy, 1912													
Diet A	July 16–17	44·3	11·13	2·86	4·92	3·35	25·1	25·7	44·2	30·1	74·3	6·3	93·7
,,	,, 17–18	9·0	1·31	0·72	0·42	0·17	14·6	55·0	32·1	12·9	45·0	0·7	99·3
,,	,, 18–19	8·9	1·60	0·79	0·37	0·44	18·0	49·4	23·1	27·5	50·6	0·9	99·1
,,	,, 19–20	12·0	1·31	0·68	0·22	0·41	10·9	51·9	16·8	31·3	48·1	0·7	99·3

October 23. No stool on this day.

Some other Analyses of the Faeces of H. C.

It will be of interest to bring into comparison with the tabulated results some figures which were kindly furnished to us by Dr. Cammidge and Dr. Karl Fürth.

Dr. Cammidge obtained the following percentages in the stool which he examined in January, 1911, when the boy was taking a milk diet:

Organic matter	87·0 %	of the dried faeces.
Total fat	83·1 %	„ „ „
Unsaponified fat	37·2 %	„ „ „
Saponified fat	45·9 %	„ „ „
Organic matter, not fat	3·9 %	„ „ „
Inorganic ash	13·0 %	„ „ „

It will be noticed that the percentage of total fat in the dried faeces closely agrees with our average.

Dr. Fürth wrote as follows: 'The boy H. C. was in the German Hospital from December 12, 1907, to June 3, 1908. We made three examinations. First in January, with an ordinary mixed diet. The dried residue of the twenty-four hours' faeces contained 90 per cent. of fat. On January 13, on a pure milk diet, and after giving Pankreon for ten days, we found 48 per cent. of fat. On account of diarrhoea we stopped the Pankreon, and gave it again in March, in 20-grain doses, for about a fortnight. Then we found, with an ordinary diet but containing as little fat as possible, 34 per cent. of fat in the faeces.' The boy gained 2½ lb. during his stay in the German Hospital. On June 1, 1908, when his age was four years and three months, his weight was 36 lb. Galton's average for a boy of the same age is 37 lb.

Discussion of the Analyses.

When the tables of analyses are examined the first point which attracts attention is the contrast between the patient H. C. and the control boy in respect of the utilization of fat. Although they were taking the same weighed diet, the control boy utilized no less than 99·2 per cent. of the fat which he took, whereas H. C. utilized only 76 per cent. and excreted 24 per cent. with his stools. However, the results obtained with the control are not in full accord with the published figures for normal adults, who have excreted, as a rule, some 5 or 6 per cent. of the fat taken.

A like contrast between the two boys is observed in the percentages of fats in the dried faeces, which in H. C.'s case reached the high figure of 79·4 per cent., but in the control case amounted only to 14·5 per cent. With normal adults the percentage has varied between 21 and 28 per cent. This ratio is, of course, influenced by the nature of the diet and the amount of residue derived from its non-fatty constituents, but identity of diet renders our results strictly

comparable, and the amount of residue other than fat differs but little in the two cases. This points to the absence of any material defect of protein assimilation which would tend to increase this residue.

In the case of H. C., so long as he was taking Diet A, the percentage of total fat, which includes fatty acids and fat in soaps, remained remarkably constant, at about 80, and that too when he was taking Fel Bovinum, Sodium glycocholate, and Pankreon. Moreover, except in the enormous Holadin stool of May 11, the residue other than fat varied but little from day to day, as long as Diet A was taken. This is of importance, as indicating that the distribution of faecal material in the daily stools was fairly uniform. The greater residue when Diet B was taken was doubtless due to the jam which was substituted for the dripping of Diet A.

The utilization columns reveal the important fact that when the fat in the diet was reduced by about one-half the percentage of fat taken which reappeared in the faeces was practically unchanged. From this it appears that increase of fat in the diet does not bring about any progressive failure of utilization, but that whatever the quantity taken the same percentage is wasted. Unfortunately the constituents of Diet C were not given in weighed quantities, and consequently the amount of fat in that diet cannot be estimated, nor the percentage utilized be determined.

Precisely similar results have recently been obtained by Oskar Gross (10) in the case of a patient with steatorrhoea, and who was believed, on good clinical evidence, to be suffering from pancreatic disease. This man, when he took a diet containing 750 grm. of fat per diem, excreted 55·4 per cent. thereof in his faeces, and when the fat taken was reduced to 168 grm. wasted 52·4 per cent. of that amount. Gross adds : ' Ich möchte diese beiden Versuche nur als Beispiele anführen und bemerken, dass auch bei fettreicher Diät und möglichst fettarmer Kost die Resultate bezüglich der prozentualen Verhältnisse im allgemeinen dieselben waren.'

Further observations on cases of various kinds are much to be desired, in order to determine whether this holds good for fat absorption in general, or is a peculiarity of any special group of cases. The explanation of the constancy of the percentage wasted is not obvious, but it appears to us, at first sight, to suggest a deficiency of some agent which influences or controls fat absorption, rather than a limitation of the absorptive power of the intestinal walls.

Although the utilization of fats by the patient H. C. is obviously much impaired, the percentage of fat which he wastes is considerably less than that lost in most cases of true steatorrhoea which have been investigated hitherto. In cases of steatorrhoea with pancreatic disease percentage losses of from 50 per cent. upwards have been observed, and occlusion of both biliary and pancreatic ducts tends to bring about still greater losses of fat, up to 70 and 80 per cent. Brugsch (11) states that obstruction of the bile-ducts alone may entail a loss up to 45 per cent., but considers that when this figure is passed implication of the

pancreas is indicated. However, the cutting off of the bile does not induce steatorrhoea, and a striking feature of our case is the occurrence of true steatorrhoea with a percentage loss of only some 25 per cent. of the fat taken.

The figures obtained in the case of H. C., when he was taking Diet B, bear a remarkably close resemblance to the averages for three cases of obstructive jaundice given by A. Schmidt and Strasburger, as the following comparison shows:

	% of total fats in dried faeces.	Total fat in faeces of 3 days.	% of fat not utilized.	% of fat split.
H. C. on Diet B	55·5	63·23	25·9	68·0
Schmidt and Strasburger average of 3 cases.	48·65	64·83	25·89	66·84

The resemblance is emphasized by the fact that the quantity of fat in Diet B (92 grm.) differs but slightly from that in the test diet given in the cases of biliary obstruction (83·5 grm.).

In cases of impaired intestinal absorption Schmidt and Strasburger (12) estimated an average loss of 17·13 per cent. of the fat taken, and F. von Müller, in a case of lardaceous disease of the intestine, a loss of 32·9 per cent., but there the percentage of fat in the dried faeces was not more than 28·6.

It will be evident, from these comparisons, that the percentage of the fat of the food which is excreted by our patient in his faeces does not throw any clear light upon the origin of the steatorrhoea, save that it is much smaller than might be expected if the functions of the pancreas in promoting fat absorption were wholly in abeyance, and is greater than is to be expected in cases of impaired intestinal absorption, unless some grave lesion of the intestinal wall, such as lardaceous disease, be present.

Biliary obstruction, of which the effects are so closely simulated, may certainly be excluded in his case.

The next point which calls for consideration is the degree to which the splitting of the fats is carried out, so far as this can be judged from the relative amounts of neutral fats, fatty acids, and soaps in the faeces.

Since the publication, in 1887, of F. von Müller's (13) classical researches on jaundice much more importance has been attached to a deficient splitting of fats than to the actual failure to utilize fats as evidence of disease of the pancreas. The pancreatic lipase plays so important a part in this connexion that we should naturally expect that when it is wanting, the process of saponification will be seriously impaired, and that the neutral fats of the faeces are excessive in amount in some cases of pancreatic disease cannot be questioned. From the investigation of a series of cases Katz (14) arrived at the conclusion that one is justified in suspecting an affection of the pancreas in cases in which less than 70 per cent. of the fat in the faeces is in the form of fatty acids and soaps, provided always that the patient is not an infant, nor the subject of a profuse diarrhoea. In the latter case the excessive peristalsis does not allow time for the fats to be adequately dealt with. Katz also found that a sudden occlusion

of the pancreatic duct inhibited fat splitting more effectually than did a more gradual cutting off of the secretion. Other observers, including Weintraud (15) and Pribram (16), have obtained similar results.

Deucher (17), on the other hand, found no excessive proportion of neutral fat in the stools in two cases of carcinoma of the head of the pancreas in which utilization was gravely impaired, and in one of which the waste of fat exceeded 80 per cent.; and Vaughan Harley (18) and Oskar Gross have made similar observations in cases of pancreatic steatorrhoea. On the other hand, Whipple (19) has described a case in which the conspicuous failure of fat absorption was apparently due to a lesion, of a quite unusual nature, of the intestinal walls. After death the pancreas was found not to be diseased, but of the fatty substances which constituted 80 per cent. of the dried faeces no less than 62·5 per cent. consisted of neutral fat.

The stools are described as white and creamy, and as having a smooth, silky appearance, and there would appear to have been no true steatorrhoea in this case.

These conflicting results have led recent observers to attach less importance to the relative proportions of fats, fatty acids, and soaps in the faeces, and more importance to the degree of utilization of fats, as indicating whether or no the pancreas is at fault. It is clear that as regards the proportions of split and unsplit fats other influences than that of the pancreatic lipase must come into play, such as the readier absorption of saponified fats, the action of intestinal bacteria, and possibly of other secretions than that of the pancreas. The smaller the total quantity of fat in the stools the more obvious should we expect the working of these influences to be, and on that account we attach little importance to the high percentage of neutral fat in the faeces of our control boy, whose total output of fat was so minute.

In the case of H. C., when Diet B (92 grm. of fat) was taken, 68 per cent. of the faecal fat was in the forms of fatty acids and soaps, and there was no conspicuous failure of fat-splitting; but when Diet A (177 grm. of fat) was taken the percentage of split fat was very much lower, viz. 38·6 per cent. To this fact we attribute the steatorrhoea in his case, for true steatorrhoea may only occur in pancreatic cases when a diet rich in fat is being taken. In this respect our case differs from Gross's, which it resembles in that the percentage of fat wasted was constant on all diets. Gross found the following proportions of fatty substances in the faeces:

	Neutral fat. %	Fatty acids. %	Fat in soaps. %
On a diet containing 750 grm. of fat .	38·7	56·8	4·5
On a diet containing 168 grm. of fat .	34·5	61·6	3·9

whereas in our case the percentages obtained were:

On a diet containing 177 grm. of fat .	61·4	32·6	6·0
On a diet containing 92 grm. of fat .	32·0	45·5	22·5

Thus on the diet poor in fat H. C. behaved like a patient with biliary obstruction, whereas when the fat in the food was doubled the percentage of neutral fat in his stools was such as is seen in cases of pancreatic disease. Yet it is evident that in this case the deficient utilization of fat was not due to deficient splitting, seeing that when the percentage of neutral fat fell, as it did on Diet B, and when certain preparations were given, the percentage lost remained unaltered.

Since in some cases of pancreatic disease large amounts of fat are excreted, and true steatorrhoea may occur, apart from any obvious defect of fat-splitting, it has been suggested (20), and the view has much to be said in its favour, that an internal secretion of the pancreas, as well as the external, plays an important part in regulating the utilization of fats.

Zoja (21) attaches much importance to scantiness of soaps in the faeces as affording evidence of disease of the pancreas, and it is interesting to note the far higher percentage of soaps in the stools of our patient when he was taking a diet poor in fat, and when he approximated more closely to the normal standard.

There remain to be considered the effects of the several preparations which were administered during periods in which the boy was taking Diet A.

The administration of the brown variety of Fel Bovinum had no obvious effect upon fat-splitting, fat utilization, nor the percentage of total fat in the dried faeces. Sodium glycocholate was equally inert. The green variety of Fel Bovinum improved the splitting, but had no influence upon the absorption of fats.

Pankreon and Holadin improved fat-splitting, but appeared to aggravate the defect of utilization. However, the trials of Pankreon and Holadin were less satisfactory than those of the bile-derivatives, and we much regret that, owing to circumstances beyond our control, we were unable to make daily analyses whilst these preparations were being taken over longer periods, and in larger doses, with simultaneous administration of alkalis.

The conclusion seems to be justified, at any rate, that none of the preparations given had any appreciable effect in controlling the error here present.

Only by the almost complete exclusion of fat from the diet could the stools be brought to assume a normal appearance and consistence, and could their fat content be brought within normal limits. But seeing that 75 per cent. of all fat taken was utilized, it is obvious that such a plan of treatment is not to be recommended.

To sum up, our investigations fail to throw any clear light upon the nature of the error of fat utilization in this case. The error is obviously one of fat absorption, accompanied by, but not dependent upon, a limitation of the power to split fats. The least unlikely explanation appears to us to be that some function of the pancreas is in abeyance. The intimate clinical association of true steatorrhoea with lesions of the pancreas favours this view, as also does the conspicuous defect of fat-splitting on a diet rich in fat, and the failure of pancreas preparations does not disprove it. In Oskar Gross's cases such prepara-

tions had no effect upon the absorption of fats, although they conspicuously improved the utilization of proteins.

The different behaviour of cases of pancreatic disease as regards fat absorption and saponification, and the uncertain results of tests of the efficiency of the gland, need excite no surprise. The pancreas is the seat of diverse morbid processes of widely different characters, some of which cause blockage of its duct, whilst others induce changes in its secreting structure, and others again do both. We can no more look for uniform clinical signs in all disorders of this gland than in such widely separated conditions as cholelithiasis and hydatid of the liver.

Summary.

A boy, aged 8 years, has been subject from infancy to true steatorrhoea, i. e. the passage from the bowel of liquid fat, which solidifies on cooling. He is the second of a family of five children of parents who are first cousins. The fifth child, also a boy, who died at the age of eleven months, was similarly affected from birth.

The boy exhibits no other morbid symptoms, is well grown and nourished, and in no way infantile.

There are no signs of pancreatic disease, unless the steatorrhoea be such. He has never been jaundiced, and cholalic acid can be detected in his faeces. He has no diarrhoea, nor other manifestations of disease of the intestines, and on a diet containing very little fat his stools assume a normal appearance and consistence.

Analyses of the stools show that of the fat which he takes by the mouth he excretes some 25 per cent. in his stools, and this percentage of loss is maintained when the fat in his diet is doubled. In other words, the percentage wasted is independent of the amount taken.

On a constant mixed diet, containing 177 grm. of fat, the total fat in the dried faeces, as neutral fats, fatty acids, and soaps, varies but little on either side of 80 per cent.

When the diet is rich in fat, the splitting of fats is conspicuously impaired, and with an intake of 177 grm. the neutral fat in the stools exceeds 60 per cent. of the total fat; but when the fat in the diet is reduced to 92 grm., the ratio of split to unsplit fat in the faeces is not excessive.

Improved saponification is not followed by improved absorption, and it is evident that the impairment of absorption is not dependent upon deficient splitting of fats.

Neither Fel Bovinum, Sodium glycocholate, Pankreon, nor Holadin brought about any improvement of utilization of fats. Some of these preparations increased the fat-splitting, but the pancreas preparations, although they had this effect, appeared to aggravate the defect of absorption.

The boy is presumably the subject of a rare inborn error of fat absorption, probably a Mendelian recessive characteristic, but our investigations have not enabled us to determine where this error lies.

REFERENCES.

1. Kunzmann, *Journal der prakt. Heilkunde*, 1824, lix, 3. Stück, 45.
2. Bright, R., *Medico-chirurgical Trans.*, Lond., 1833, xviii. 1.
3. Tulpius, Nicolas, *Observationum Medicarum Lib. iii*, cap. 18.
4. Salomon, H., *Die deutsche Klinik*, xii (Ergänzungsband 1), 533.
5. Walker, T. J., *Medico-chir. Trans.*, Lond., 1889, lxxii. 257.
6. Finizio, G., *La Pediatria*, Napoli, 1909, 2nd ser., vii. 674.
7. Home, Sir Everard, *Phil. Trans. Royal Soc.*, 1813, ciii, Part 2, 152
8. Loewi, O., *Archiv f. exper. Path. und Pharmakol.*, Leipzig, 1908, lix. 83.
9. Garrod, A. E., *Lancet*, Lond., 1908, ii. 5.
10. Gross, Oskar, *Deutsches Archiv f. klin. Med.*, 1912, cviii. 106.
11. Brugsch, T., *Zeitschr. f. klin. Med.*, Berlin, 1906, lviii. 518; *Zeitschr. f. exper. Path. und Ther.*, Berlin, 1909, vi. 326. See also Glaessner, *Ergebnisse der inneren Med. u. Kinderheilk.*, Berlin, 1910, vi. 56.
12. Schmidt, A. und Strasburger, *Die Faeces des Menschen*, Berlin, 2nd edit., 1905, 161.
13. Müller, F. von, *Zeitschr. f. klin. Med.*, Berlin, 1887, xii. 45.
14. Katz, A., *Wiener med. Woch.*, 1889, xlix. 153, 214, 266.
15. Weintraud, *Die Heilkunde*, Wien, 1898, iii. 67.
16. Pribram, *Prager med. Woch.*, 1899, xxiv. 463, 476.
17. Deucher, P., *Correspondenzblatt f. schweiz. Aerzte*, Basel, 1898, xxviii. 321 and 361.
18. Harley, Vaughan, *Journ. Path. and Bacteriol.*, Edinb. and Lond., 1896, iii. 245.
19. Whipple, G. H., *Johns Hopkins Hosp. Bull.*, Baltimore, 1907, xviii. 382.
20. Falta, W., *Zeitschr. f. klin. Med.*, Berlin, 1910, lxxi. 17, and Gross, O., loc. cit. sub 10.
21. Zoja, L., *Il Morgagni*, 1898, xl, Pt. 1, 617, and 1899, xli, Pt. 1, 1. (Full bibliography of fat-absorption.)

See also *re* Steatorrhoea with disease of the Pancreas:

Oser, L., 'Die Erkrankungen des Pankreas', *Nothnagels Specielle Pathol. u. Therapie*, 1898, 89.

Gigon, A., *Zeitschr. f. klin. Med.*, Berlin, 1907, lxiii. 420.

Glaessner, K., und Sigel, J., *Berl. klin. Woch.*, 1904, xli. 440.

CRITICAL REVIEW

ARTIFICIAL PNEUMOTHORAX

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§ 1. *Historical Sketch.*

The idea of inducing more or less permanent collapse of a tuberculous lung, by means of an artificial pneumothorax, in order to influence the disease favourably, is much older than one would think. It is interesting to notice how often attempts—some of them very remarkable—have been made in various countries during the last century towards the realization of that idea. They all fell into oblivion. Only during the last four or five years have the strenuous efforts of several physicians succeeded in forcing general attention to such a degree that artificial pneumothorax has become the topic of the day in phthisiological literature.

Historically, England leads the way. James Carson (of Liverpool), nearly a hundred years ago, was, I think, the first who conceived the possibility of using pneumothorax as a therapeutic measure—the first too who, from original and well-conducted physiological experiments, deduced a clear and correct view of the part played in respiratory mechanics by the elasticity of the lungs. Even in the best modern text-books it would be difficult to find a more admirable description than the following one, which I quote from his communication to the Royal Society in 1819: 'Two powers are therefore concerned in regulating the movements and in varying the dimensions and the form of the diaphragm, the elasticity of the lungs, and the contractile power of the muscular fibres of the diaphragm. Of these powers the one is permanent and equable, the other variable and exerted at intervals. The contractile power of the diaphragm, when fully exerted, is evidently much stronger than its antagonist, the resilience of the lungs; but the latter, not being subject to exhaustion, takes advantage of the necessary relaxation of the former, and rebounding, like the stone of Sisyphus, recovers its lost ground, and renews the toil of its more powerful opponent. Breathing is in a great measure the effect of this interminable contest between the elasticity of the lungs and the irritability of the diaphragm' (10).

Carson measured the pressure which balances the elasticity of the lung by exactly the same method which Donders, who still has the credit of having

initiated those researches, imagined only thirty-four years later. In another paper, read before the Medical Society of Liverpool in 1821, he explained by the action of lung elasticity the slow and difficult cicatrization of lesions and abscesses located in the lung parenchyma; and, having showed that rabbits recover easily from artificially induced pneumothorax, he concluded that collapse of the lung suppressing its elasticity would be a secure, simple, and complete remedy of suppurative lesions or cavities of the organ. He even suggested the possibility of establishing successively pneumothorax on both sides at a reasonably long interval, in case the lesions should be bilateral (11).

I could not find any evidence that Carson ever attempted a practical realization of his theoretical views. But, some years later, Ramadge seems to have purposely punctured the pleural cavity in a case of ulcerous phthisis, in order to diminish the capacity of the thorax and consequently to compress the lung. His ideas were evidently of a much vaguer nature than Carson's. He imagined that, through the puncture opening, air was expelled from the lung outside. Nevertheless his patient was alive and doing well two years after the operation. Ramadge's views did not attract any notice.[1]

The question was no more ventilated till the advent of antiseptic surgery, when we hear of several attempts. Cayley (1885) tried to cure a severe haemoptysis by producing lung collapse. 'The left side of the patient's chest was flattened in front, and the expansion was much diminished. There was dullness on percussion over the scapular region, and here there was feeble bronchial breathing. The breath sounds all over this lung were very faint and accompanied by moist râles. These signs were attributed to the lung being clogged with blood. On the right side the physical signs were normal.... As it was now evident that much repetition of the haemorrhage, in all probability due to a pulmonary aneurysm or to the ulceration of a large vessel, must prove fatal, *it was determined to induce pneumothorax, with the expectation that the great diminution of the circulation through the collapsed lung, together with the pressure exercised by the air, would arrest the haemorrhage; and supposing there was active development of tubercle in progress in the lung, this would probably*

[1] Ramadge had a temporary fame of a rather unpleasant kind. In the *Sunday Times*, April 10, 1831, he imprudently published a letter containing an apology of a quack's book and virulent attacks against several medical men. He was in consequence absolutely boycotted by the medical profession, who declined to meet him in consultation. A letter signed 'One', in the *Lancet*, described a scandalous scene at a patient's bed, between Ramadge and a Dr. Tweedie, who said that 'no medical man of respectability would call Ramadge or consult with him, without injuring himself in the eyes of his brethren'. Ramadge sued the *Lancet* for libel; several medical men came as witnesses, and said they would decline to meet Ramadge. The editor was fined one farthing. Curiously enough, the *London Medical and Surgical Journal*, where the libel had been reproduced, was fined £400 by another judge. The whole affair seems to have caused a considerable stir at the time. No wonder Ramadge's opinions on the treatment of tuberculosis were not appreciated by his contemporaries. (See *London Med. and Surg. Journ.*, 1832, vol. i, Sat. July 7, pp. 711–727). His book appeared two years later under the title: 'Treatise on the Nature and Treatment of Pulmonary Consumption.' A French translation was published in 1836, at Brussels.

for a time be checked. . . . Accordingly, at 6 p.m. on March 10, Mr. Hulke made an incision in the sixth intercostal space, an inch behind the anterior fold of the axilla, and introduced into the pleural cavity a double tube, made by uniting together by a shield two pieces of elastic catheter about three inches long. The opening was protected by a small cage, lined with carbolic gauze, and the whole covered by a carbolized gauzed bandage. The air passed freely in and out at the time of the operation, and the apex of the heart moved to the mid-sternal region. . . . The resonance became tympanitic, and the bell-sound could be elicited. There was no return of the haemorrhage. On March 15 the patient died quite suddenly, apparently from syncope. After death both lungs were found studded with recent grey miliary granules. In the lower part of the upper left lobe was a cavity the size of a walnut, filled, except at its centre, by a light-coloured laminated clot. In the centre of this clot was a small round cavity containing a little loose black coagulum, and this cavity communicated with a considerable branch of the pulmonary artery. A large bronchial tube opened into the periphery of the pulmonary cavity . . .' (12).

Cayley's daring attempt came at a time when enlightened medical opinion was quite prepared to accept it. He read a report of his case at the Clinical Society of London, and met with much applause and encouragement. The discussion which followed his paper is very interesting. Duffin 'did not think we need be afraid of the admission of air into the pleura ; physiologically we should expect valuable results to follow the operation'. R. W. Parker 'thought the treatment was rational, but there were ways of causing pneumothorax without running risks from septic agencies. He recommended the injection of filtered and carbolized air into the pleura such as he had advised in the treatment of certain kinds of empyema. A hypodermic syringe with an elastic ball and some carbolized cotton-wool were the only articles required for the operation.' Charles Symonds spoke of the induction of artificial pneumothorax 'as having been suggested by Mahomed in a case on which they had held a consultation. The aim of the operation was to be the arrest of phthisis.' Ewart considered that 'an important departure in the treatment of pulmonary cavities might date from Cayley's recommendations. He remembered that some time ago Douglas Powell had induced artificial pneumothorax for the treatment of a large cavity. The upper lobe had been almost entirely destroyed, and the cavity in it had been practically obliterated, as the autopsy showed. The lower lobe of the lung was practically carnified ; there was an empyema, and aseptic air was introduced as a means of treating the empyema, and at the same time with a view of causing collapse of a pulmonary cavity.'

This discussion at the Clinical Society of London, which I quote on purpose at some length, shows that the idea of inducing pneumothorax as a therapeutic measure seemed quite rational to medical minds, in England at least, in the eighties. If a faultless and efficient technique had been invented by Cayley, the collapse-method would probably have progressed more rapidly and have met with much less opposition and scepticism than it has in our days.

At the same period, and quite independently from Cayley, pneumothorax was regarded as a possible cure for certain forms of phthisis in France. Carson's, Cayley's, and even Ramadge's arguments were founded exclusively on physiological considerations. Clinical experience led Potain to the same idea. Stokes had already observed that 'in many cases, where the disease (pneumothorax) becomes chronic, we may observe a singular suspension of the usual symptoms of phthisis. The phthisical countenance disappears; the sweats cease; the pulse I have known in some cases to become quiet, and the patient may gain flesh and strength to a surprising degree' (59). Houghton (60), Stokes's contemporary, had made similar remarks. But, in the middle of the last century, the opinion seemed to prevail that tuberculous pneumothorax was always and absolutely fatal. As late as 1887, Rühle (49), summarizing the opinions of his contemporaries, could write in Ziemssen's *Handbook*: 'A tuberculous pneumothorax of long duration belongs to the rarities; but there is so far no example of a healed pneumothorax coincident with recovery of a lung tuberculosis.' Hérard (30) was the first to observe again that pneumothorax does not always kill a tuberculous patient, nay, that it may even favour the healing of tuberculous lesions. At the French Congress of Algiers (1881) he published two very striking histories, where the curative influence of spontaneous hydropneumothorax in tuberculous cavities of the lung was verified by autopsy. Adams (1) in England, Späth (56) in Germany, wrote to the same effect. Potain (44) went further. He deliberately injected sterilized air into the pleural cavity in three cases of spontaneous pneumothorax with liquid effusion. His idea was that collapse of the lung was beneficial because it immobilized the organ; to let it expand again would mean putting an end to that immobilization, and giving a new stimulus to lesions. Therefore the only rational conduct was to tap the liquid and to inject air into the pleural cavity. 'Le pneumothorax est une maladie *qu'il ne faut pas guérir*' (Pneumothorax is a disease one *ought not* to cure). Of Potain's three patients, only one, with bilateral phthisis, died after a temporary improvement. The two others were absolutely restored to health. The first of these successful cases had been treated in 1885; when Potain saw him again in 1886 he had returned to his former profession of a *singer*. The second one had had Koch's bacilli in his sputum—a then new test—and severe lung lesions with tubular breathing and numerous moist crackling râles: the bacilli at the end of the treatment—288 days, with three air-injections—completely disappeared, together with the physical signs.

Potain, for many years, was busy with the problem of curative pneumothorax. His three patients were operated with a trocar connected with a manometer, and he very accurately measured the intrapleural pressure. He made many researches on the capacity of absorption of divers gases, and finally concluded that nitrogen was the least rapidly absorbed. He performed experimental pneumothorax on a great number of rabbits, devised several specimens of trocars, and, in his clinical teaching, constantly referred to the possibility of curing phthisis by artificial pneumothorax.

Notwithstanding Potain's undisputed and legitimate authority, he found no followers. There is no doubt that he was the first to deliberately inject gas into the pleural cavity. His therapeutic results were strikingly good. They were accepted with utter indifference. As late as 1901, Lucius Spengler (57), who has been since one of the most deserving advocates of artificial pneumothorax, wrote about Potain's achievements in a quite desultory way, and considered his method of treating spontaneous pneumothorax as perfectly useless and much too complicated.[2]

Forlanini's theoretical considerations on the mechanism of caseation and ulceration in phthisis, and on the favourable influence of spontaneous pneumothorax, are contemporaneous with the above-quoted French researches, and partly inspired by them. Toussaint's (63), a pupil of Potain's, dissertation seems especially to have stirred the Italian physician's thoughts. His first paper, published in 1882 (20), dealt with the dependence of ulcerative processes in the lung upon mechanical causes and showed that pleural effusion or spontaneous pneumothorax often result in an arrest of the phthisical process; the arrest is generally only a temporary one, the immobilization of the lung by the gaseous or liquid effusion being itself only temporary. Therefore it seemed advisable to immobilize permanently the lung; artificial pneumothorax was, theoretically, the best way. Forlanini's proposal 'excited no interest and met with no approval', to quote his own words. Only in 1888 did he, for the first time, inject air into a pleural effusion, in a case of one-sided phthisis (21); and only in 1894, at the eleventh International Congress of Medicine in Rome, did he publish his first two cases of artificial pneumothorax (22). The next year he made another communication on the subject at the Italian Congress for Internal Medicine (Rome, October, 1895) and reported one case of advanced phthisis cured by artificial pneumothorax (23). He described his technique, which, as we shall see later on, was not fit to inspire great confidence. Nobody, in Italy or elsewhere, felt encouraged to follow his example. Forlanini himself kept silent till 1906.

During this interval of twelve years, an important step was made in the United States by J. B. Murphy, of Chicago (41), a surgeon, the first and only surgeon who contributed to our subject. At the meeting of the American Medical Association in 1898 he presented an important 'Oration' on 'Surgery of the Lung', where, among many other topics, he gave an account of his attempts at influencing pulmonary tuberculosis by artificial pneumothorax. He approached the question in a very surgeon-like fashion, as the following characteristic quotation will show: 'Tuberculosis of the lung has been considered a medical and not a surgical disease. In a few instances the surgeon has had the courage to open and drain cavities in the lung. . . . With these few exceptions, the disease has been left entirely to the care of the physicians. We ask ourselves, What has been achieved in tuberculosis? With the exception of

[2] 'Man denke nur an die Sterilisation der einzupumpenden Luft!' is one of Spengler's weightiest objections.

a thorough knowledge of its etiology and pathology, comparatively nothing. . . . From a therapeutic standpoint, we had hoped, and still hope, that tuberculosis may be cured, alleviated, or curtailed in its destructive effects by products derived by the tubercular bacillus under certain conditions. The results barely justify a continuation of that hope. Can surgery contribute anything toward the repair of tubercular lesions of the lung? . . .'

Murphy then explains how he was led to the idea of producing collapse of the tuberculous lung, and I don't think the arguments in favour of that therapy can be put in clearer and more concise words than his: 'The pathology of repair of pulmonary tubercular cavities involves certain physical conditions which are peculiar to the chest . . . namely, the constant resistance of the bony framework against contraction, the effort at expansion of the cavity in each respiratory act. The best illustrations exist in large empyemic cavities. . . . Allow the wall of the abscess to collapse, to empty thoroughly, and it will heal as other abscesses of the same pathologic character; this, I believe, is the key-note to the successful treatment of pulmonary cavities. How to overcome this resistance of the chest wall was a stimulus to my investigations in lung surgery, and led to the hope that not only might pulmonary cavities be obliterated by permitting or forcing their collapse, but that primary tuberculosis might be encapsulated by mechanical immobilization of the diseased portion by collapse and enforced rest of the lung as a respiratory apparatus, thus allowing the cicatrization and encapsulation of the tubercular foci; in other words, that tuberculosis of the lung might be treated as we treat tuberculosis of the joints, by immobilizing and enforcing physiologic rest, by enforcing drainage of the secondary products through the bronchi and allowing the ulcer or cavity to heal. . . .

'The methods of obtaining pulmonary quiescence or collapse are: (1) by permitting or forcing the collapse of the lung by separation of the parietal pleura and intrathoracic compression (extrapleural pneumothorax); (2) by removing the bony resistance and allowing the collapse of the chest wall, thus favouring contraction and cicatrization (thoracoplasty); (3) allowing the lung to collapse by intrapleural injection of gas or fluid. The third method appears to offer more than any others.'

Murphy calls attention to the fact that traumatic pneumothorax is very seldom a dangerous occurrence. Out of a total number of 11,540 chest-wounds observed during the American Civil War, there were severe complications due to pneumothorax in less than half a dozen cases only (Paget). He himself, during twenty years of hospital surgical practice, has seen only two cases where pneumothorax was the cause of 'unpleasant symptoms'. This shows that artificial pneumothorax can be induced safely. Moreover, 'we know that atelectasis of the lung may exist for months or even years, and the lung be again restored to its function.'

I shall refer later on to Murphy's technique, which is very simple—even a little too simple; it essentially consists in introducing nitrogen into the

pleural space through a trocar. He tried it in five cases, two of which were failures, pleural adhesions preventing the gas from penetrating. In the three other cases the results were, as it seems, excellent. But unfortunately the histories are very incomplete and the patients seem to have been followed for a short time only after pneumothorax had been induced.

The following year, Lemke (37), a pupil of Murphy's, reported fifty-three cases of pulmonary tuberculosis treated with intrapleural injections of nitrogen. The histories are a little more detailed than Murphy's, but not much. The greater number of patients had relative dullness of the right or left apex, with more or less numerous crepitant râles and bacilli in their sputum. Very few among them had cavities, which explains perhaps that Lemke met only four cases where adhesions prevented the introduction of nitrogen into the pleural space. In a majority of cases the result was a considerable improvement, sometimes after two or three, or even only one injection. In some of them it is mentioned that there was a considerable diminution of expectoration, that the bacilli disappeared, that the fever subsided. Lemke had one severe accident: a right-sided hemiplegia with motor aphasia, of one month's duration, evidently caused by gas embolism.

His report does not seem to have met with any success at the meeting of the American Medical Association. The discussion which followed shows that the importance of the new method was not understood. Yet Lemke was not the only one in the United States to have been stirred by Murphy's report. He himself mentioned six cases treated by C. P. Thomas (of Spokane, Wash.); and Schell (54) (of Terre-Haute, Indiana) had, the year before, injected 85 cubic inches of nitrogen into the pleura of a patient affected with severe haemoptysis.

Lemke died soon after publishing his cases, and Murphy, although repeatedly urged to use the method, and fully convinced of its scientific value, persistently refused to do so because it would take him out of surgery into medicine (36). This resulted in the complete neglect of collapse therapy of lung tuberculosis in America, till the method was imported into the States from Germany, quite recently.

Still Murphy's and Lemke's labours were not lost. Their work attracted the attention of Brauer, then professor at Marburg, who took a keen interest in collapse therapy, and, on December 20, 1905, reported to the 'Aerztlicher Verein' at Marburg his first case of artificial pneumothorax, 'nach Murphy' (2). In 1906 he published a second case in the *Deutsche medizinische Wochenschrift* (3). The description of it is given with the utmost care and thoroughness. A woman, who had a cavity in the left lung, was injected with 1,600 c.c. of nitrogen under negative pressure, and, after a month had elapsed, 1,800 c.c. under a positive pressure of 8 cm. of water; a third and a fourth injection had been made when the case was published. After each introduction of nitrogen the fever subsided and the bronchial discharge was reduced to a minimum. The final result was a very remarkable one, which would have been unattainable with any other method.

A. Schmidt (55) reported a similar case, the same year, also in the *Deutsche medizinische Wochenschrift.*

Then, at last, Forlanini (of Pavia) broke his long silence and claimed a right of priority in the invention of artificial pneumothorax. He gave an account of twenty-five cases of pulmonary tuberculosis which he had treated during the interval of twelve years since his last publication, and briefly described his technique, which, he said, was as simple as an ordinary hypodermic injection (24).

However meritorious Forlanini's efforts have been, and however gratifying it must be for him to see his idea triumphantly realized thirty years after he first conceived it, it cannot be denied that Brauer owed nothing to the Italian professor, that he got his idea from Murphy (who was not aware of Forlanini's attempts), and that it was through Brauer's impulse that collapse therapy has become a rational and methodical procedure. Although Brauer's own method is being more and more abandoned, it is due to his and his pupils' work that safer methods have been devised, and that physicians all over the world have been encouraged to treat pulmonary tuberculosis with artificial pneumothorax.

Indeed, since Brauer took up pneumothorax therapy, it has not only been applied by a great number of physicians in the German countries, in Switzerland, and in Scandinavia, but it has come back to the country of Potain through Dumarest, P. Courmont, and especially through G. Küss (of Angicourt); it has returned to the country of Murphy, thanks to S. Robinson, Cleaveland Floyd, and Mary E. Lapham; and, last but not least, it found its way, with Colebrook and Lillingston, to the country of Carson and Cayley.

§ 2. *Murphy's, Lemke's, and Forlanini's Technique.*

Murphy used a very simple instrument for his nitrogen injections: it was a system of two bottles communicating through an india-rubber tube; bottle No. 1 was connected through a first tube with an india-rubber bag full of nitrogen, through a second tube with a trocar; it was filled up with sterile water and placed at a higher level than bottle No. 2. By opening the communication with the nitrogen bag, the gas was allowed to penetrate into No. 1 and to drive the water into No. 2. The communication with the nitrogen bag was then blocked, and the water containing bottle No. 2 placed at a higher level than the gas containing No. 1. The apparatus was ready for use.

'The chest wall', says Murphy, 'should be thoroughly cleansed and rendered aseptic. Chloride of ethyl should be used for local anaesthesia. A tenotome puncture should be made through the derma; this allows the trocar to be easily inserted. The stilette in the trocar should be withdrawn when the rib is reached; the gas should now be turned on; the trocar should then be pushed inward, hugging the margin of the rib. When the parietal pleura is punctured, the trocar advances rapidly and the gas begins to flow freely into the cavity unless adhesions exist. If adhesions be present the gas will not flow. The

trocar should be taken out and inserted in the same manner in another position.'

Lemke used a similar apparatus. He wrote: 'The needle, which is an ordinary, spear-pointed aspiration needle, is inserted in the fifth or sixth interspace, in about the anterior axillary line, or slightly further back. . . . It is important, after the needle is inserted, and before the tube is attached, to assure oneself that the point of the needle is in the pleural cavity, and this is done by instructing the patient to take a series of deep inspirations, when, if the needle be within the pleural cavity, a current of air can be heard to rush into it. If the needle has entered the lung, as it will when the two pleural surfaces are adherent, there is a slight current of air through the needle during forced expiration, and frequently a little frothy blood will appear.'

This method, needless to say, is exceedingly dangerous. If Lemke, out of fifty-three cases, had only once an accident with embolism, it is probably, as I pointed out above, because he treated a majority of slightly advanced consumptives: he found almost always free pleural spaces with no adhesions.

Forlanini's early method was perhaps still more dangerous. His communicating bottles were not movable like Murphy's, but fixed. The consequence was that, instead of using gravity for the displacement of the water, he had to expel it from bottle No. 2 into bottle No. 1 by means of compressed air, through an india-rubber bulb. He therefore not only, like Murphy and Lemke, had absolutely no information concerning the intrapleural pressure, but he could not even measure the pressure under which nitrogen was injected into the pleura. This Murphy could do easily by measuring the difference of level of the water in his two bottles.

§ 3. *Modern Manometric Instruments.*

Brauer saw at first, when he began his studies in collapse therapy, that it was most important to be able to measure the variations of intrapleural pressure. One wants of course to know the volume of the injected gas; but the essential question is to measure the amount of pressure exerted on the external surface of the lung. Therefore it is absolutely necessary to have a manometer adjusted on the tube which communicates with the pleura. The addition of a manometer to the pneumothorax instrumentarium made the method an absolutely safe one; it transformed a blind and daring operation into a perfectly controllable, accurate, and scientific technique.

It would be tedious and aimless to give an account of the various apparatus which have been devised in recent years. Some are unnecessarily complicated. A few are very simple, easy to understand and to handle. I shall describe one of those, G. Küss's instrument, which is the most used in France (34). It will be easy to point out how far other types differ from it.

Like Murphy's and Brauer's, Küss's apparatus essentially consists of

a system of two vessels communicating at their bottom through an india-rubber tube, and where a liquid displaced by gravity displaces a gas in its turn. One is fixed; one is movable up and down. The movable one is an open bottle containing a watery solution of some antiseptic, e. g. bichloride of mercury. The surface of the liquid, in this bottle, always supports atmospheric pressure. The fixed reservoir is a graduated glass cylinder of a capacity of 500 c.c. It is tightly closed at its top by means of an india-rubber stopper. Through the stopper a glass tube establishes a communication between the cylinder and (1) an india-rubber bag where nitrogen is stored up, (2) the trocar and the manometer. Both communications can easily be interrupted by means of a cock or a forceps.

Let us suppose we interrupted the communication with the trocar and manometer, as one always must do at the beginning. By opening the communication with the nitrogen bag, which we can compress gently with the hand, we fill up the cylinder with nitrogen and displace the water into the movable bottle. We then interrupt the communication with the bag. By displacing the movable bottle vertically, we regulate the pressure of the nitrogen in the cylinder. If the surface of the liquid is at the same level in the cylinder and in the bottle, we have atmospheric pressure in the cylinder. If it is at a higher level in the bottle, we have a positive pressure in the cylinder; if it is at a lower level in the bottle, the pressure in the cylinder is inferior to the atmospheric: it is a negative pressure. The distance between the two levels, which a movable metric rule enables us always to measure, is the measure of the pressure, whether positive or negative, in centimetres of water.

The glass tube through the india-rubber stopper at the top of the glass cylinder branches into a first tube communicating, as we saw, with the nitrogen bag, and a second india-rubber tube communicating with the trocar and the manometer. On its way through this tube the gas is filtered on sterilized cotton-wool. The manometer is a simple U-shaped water manometer. Its communication with the trocar should never be interrupted. But both trocar and manometer can be disconnected from the nitrogen-containing glass cylinder.

Let us suppose our glass cylinder is filled up with nitrogen under atmospheric pressure, the level of the liquid in both reservoirs being therefore the same. We have stopped the communication between the cylinder and the trocar. We insert the trocar through the intercostal space. As soon as it has penetrated into the pleura, the manometer oscillates and shows a negative pressure, which increases during inspiration and decreases during expiration. As long as we don't see these characteristic oscillations we can be absolutely certain that the extremity of our trocar is not in the pleural space, and therefore it is useless to open the communication with the nitrogen-containing cylinder. But we can safely do so when the manometric oscillations indicate that the trocar has penetrated into the pleura. The intrapleural pressure being negative, nitrogen will penetrate into the pleura. The liquid will slowly pass from the bottle into the cylinder, till the nitrogen pressure in the cylinder is equal to the

average negative pressure in the pleura. Then the whole system will be in equipoise, the distance between the higher level of the water in the cylinder and the lower level in the bottle measuring the average negative pressure in the pleura. By moving the bottle upwards this equipoise will be disturbed; more nitrogen will penetrate into the pleura. After some time the pressure in the pleural space will be equal to atmospheric pressure, and, the system being in equipoise, the liquid will be at the same level in bottle and cylinder. It is easy to ascertain what quantity of nitrogen was necessary to convert a negative intrapleural pressure of, let us say for instance, 4 cm. of water into atmospheric pressure. It is measured by the displacement of water in the cylinder.

Once atmospheric pressure has been established in the pleura, a positive pressure in the cylinder becomes necessary in order to introduce further quantities of gas. The bottle being moved upwards, the level of the water in it will be higher than in the cylinder. The distance between the two levels always measures the pressure under which nitrogen forces its way into the pleura; the same distance, when the system is in equipoise—when, in other words, no more gas can penetrate and no more water is displaced—measures the intrapleural pressure.

With this instrument the operator is always, at any given moment, able to ascertain what the intrapleural pressure amounts to, in centimetres of water, and what pressure he uses to force the nitrogen into the pleura. It is evident also that the same instrument can be used to withdraw gas from within the pleura, in case one has established too high a positive pressure. By filling the cylinder with water, and placing the bottle at a low level, the liquid will be displaced from the cylinder into the bottle, and nitrogen coming from the pleura will take the place of the water in the cylinder.

To perform this nitrogen aspiration, Forlanini proposes to use a different instrument, specially made for that purpose—a very unnecessary complication, which is absolutely avoided by Küss's apparatus. But Forlanini's pneumothorax apparatus, as well as Saugman's and von Muralt's and many others, consists of two *fixed* vessels, into one of which air has to be compressed by means of an india-rubber bulb, in order to displace the water. This, of course, excludes the possibility of establishing a negative pressure in the system—a very serious drawback, in my opinion.

Several models of manometers are used by different authors. Brauer has a water manometer and a mercury manometer together on his apparatus; so have Saugman and Begtrup Hansen. Wellmann uses a Recklinghausen tonometer. A single water-manometer seems to be quite sufficient.

Almost every physician who did pneumothorax work has invented his own trocar or needle. I am not going to discuss their different merits. For re-injections of nitrogen into an already established pneumothorax, hollow needles are used. Some operators use them also for the first injection. But trocars are much more convenient. The best and safest ones have a sharp point to penetrate

through the skin and external intercostal muscle, and a blunt one to reach the intrapleural space through the fibres of the internal intercostal muscle. Küss's blunt stilette is hollow on one side, and when the hollow side is turned towards the lateral opening of the trocar, the cavity of the trocar communicates with the manometer.

§ 4. *The First Injection by the Incision Method.*

All authors agree in *refilling* an already established pneumothorax by means of a puncture with a hollow needle communicating with the injecting apparatus. But there is much discussion as to the best technique to be used in *initiating* an artificial pneumothorax. One has to choose between two methods: the puncture, which is generally called after Forlanini's name, and the incision, known as Brauer's or as Murphy-Brauer's method. This last appellation is quite wrong, and that it should still be used currently in pneumothorax literature, especially in Germany, shows that very few people have read Murphy's original paper. The American surgeon's method—as the reader can easily infer from the above-quoted passage—is essentially a puncture. But, as Brauer's first communication on the subject bears the title 'Die Behandlung der einseitigen Lungenphthisis mit künstlichem Pneumothorax *(nach Murphy)*', Murphy's name has become erroneously, but, I am afraid, permanently, associated with Brauer's method, which I shall now shortly describe (4).

Under local novocaine and ethyl chloride anaesthesia, and with every aseptic caution, an incision of about 5 to 7 cm. is made in the chosen intercostal space. The skin and the subcutaneous cellular tissue are cut with the knife. The intercostal muscles should rather be divided with some blunt instrument such as Cowper's scissors or a dissecting forceps. The haemostasis must be very careful. Under the intercostal muscles the parietal pleura is discovered. It is easy to see whether it is thickened or normal and transparent, whether the lung has still preserved its respiratory mobility or not. The pleura is then perforated by means of a blunt cannula provided with a side-opening. If the lung is free, one hears the whispering sound of air entering the pleura during inspiration. An elastic catheter is then introduced through the cannula, in order to explore the pleural space and to ascertain whether there are adhesions in the neighbourhood or not. If the conditions seem favourable, the cannula is connected through a sterile india-rubber tube with the manometer and the nitrogen apparatus, and the gas is allowed to enter into the pleural cavity. After a sufficient quantity has been introduced, the cannula is withdrawn, the intercostal muscles are sewn with cat-gut, the haemostasis is made complete, if necessary, by ligating bleeding vessels, and from four to six sutures are made on the cutaneous wound, which has to be dressed aseptically.

This method evidently obviates the two capital dangers of Murphy-Lemke's or Forlanini's original puncture method. It is almost impossible, says Brauer, to produce an artificial pneumothorax in the healthy dog with the puncture

method without injuring the visceral pleura. O. Bruns came to the same conclusion. Indeed the wound produced by the needle on the surface of the lung is very small, and, in the healthy individual, it is absolutely harmless. But the danger of injuring a tuberculous lung cannot be denied. Infectious material from the lung can infect the pleura, or a lung fistula can be created. It must be a rare occurrence, and I don't know of any conclusive case in the literature, except the one of Knoblauch, quoted by Brauer. Yet one has to take it into consideration.

Much more important is the danger of penetrating with the needle into a blood-vessel and creating air, or rather, *nitrogen embolism*. The gas bubbles generally pass through the pulmonary veins and the left heart to the aorta and carotid, and determine obstruction of one of the cerebral arteries, the result being immediate death or more or less permanent hemiplegia. Lemke's seventeenth case is a good illustration of this: the patient had complete right-sided hemiplegia, with aphasia, of one month's duration. Brauer and Spengler have published two cases of nitrogen embolism occurring during a first puncture, followed by death. They admit that many accidents described by Forlanini as *pleural eclampsy* were really cases of minute gas embolism. Such are sudden loss of consciousness lasting sometimes several hours, tonic and even clonic contractions often of a pronounced hemiplegic type, monoplegic or hemiplegic paralysis, &c. It is indeed very unlikely that such symptoms should have been due to pleural reflex, and it is very remarkable that authors using a better technique have never experienced them.

Although Forlanini emphatically refuses to accept this explanation of his so-called eclamptic accidents, there is no doubt that nitrogen embolism must have occurred with his original technique. If something is to be wondered at, it is that it did not occur more often. The principle of his method was to puncture with a hollow needle in permanent communication with a cylinder containing nitrogen under positive pressure. He knew his needle was in the pleural space only when he saw the level of the liquid ascending in the cylinder; in other words, when the gas entered freely. And he used no manometric measurements. A more blind and risky method can hardly be imagined, and it deserved all the criticisms of Brauer. These criticisms apply also to Murphy and Lemke's method.

§ 5. *The Modern Puncture Method.*

But the puncture method has been so considerably modified, that it has to-day very little in common with Forlanini's first technique. Saugman (52), Würtzen and Kjer-Petersen (67), von Muralt (39) and others have added a manometer to Forlanini's apparatus and shown that nitrogen must not be allowed to pass the trocar before the manometric readings indicate the penetration into a free pleural space. Forlanini himself finally took up last year the manometer which he had so bitterly criticized before, and connected his puncture

needle with a little safety syringe, allowing him to ascertain whether the needle had or had not entered a blood-vessel. The most useful and ingenious improvements have been devised by G. Küss, in whose apparatus nitrogen can be kept at will under a pressure inferior, equal, or superior to the atmosphere, and where a blunt trocar is substituted for a sharp needle. He was able to demonstrate experimentally that, with this trocar, pneumothorax can be induced on dogs without injuring the lung in the least.

I will now describe the puncture method as I practise it myself, following G. Küss's rules. The skin must be sterilized with iodine tincture, or, better still, with a 10 per cent. solution of iodine in chloroform; it has the advantage of being much less irritant, a thing to be considered, as, if the pneumothorax is successful, the same spot will have to be sterilized a great number of times during several months or years. Local anaesthesia of the chosen intercostal space is provided for by the intradermic, intracellular, and subperiostal injection of two or three cubic centimetres of a 2 per cent. solution of novocaine. To anaesthetize the skin itself, ethyl chloride should be used. A negative pressure of about 4 or 5 cm. of water is established in the nitrogen cylinder. The trocar is connected with the manometer only, through a sterilized india-rubber tube; a little glass tube is inserted between the trocar and the india-rubber tube. When anaesthesia is supposed to be complete, the skin is punctured with the trocar. As soon as the external intercostal muscle is reached, the sharp stilette is withdrawn; the blunt one is substituted for it and gently inserted through the muscles along the upper margin of the inferior rib. A special sensation of resistance overcome informs the operator that the internal intercostal muscle has been perforated.

Küss's blunt stilette being hollow on one side, the lateral opening of the trocar communicates with the manometer. As soon as the trocar opens into the pleural space, the water-column in the manometer is raised by 8 or 12 or even 15 cm., and begins to oscillate rhythmically coincident with the respiratory movements. During inspiration the negative pressure is at its maximum; during expiration it diminishes and becomes almost equal to atmospheric pressure. But the medium pressure is always negative, when the trocar opens into the pleural space. The communication with the nitrogen cylinder is then opened, and one can follow the water-level ascending in it, and measure accurately the quantity of gas which enters the pleura, the force which displaces it being the elastic retraction of the lung. After some time equipoise is obtained, the level of the water having reached a maximum. The distance between the level in the cylinder and the level in the bottle measures the negative pressure which balances the elasticity of the lung. The bottle is then gradually lifted up and more gas penetrates the pleura, under a lesser negative pressure first, then under atmospheric pressure, and finally under positive pressure. The quantity of nitrogen injected, the pressure used to inject, the pressure in the pleural cavity can be measured and followed during the whole course of the operation. When the quantity of gas injected and the intrapleural pressure

obtained are considered sufficient, the trocar is withdrawn, and the puncture wound closed with collodion.

Provided this method is followed intelligently, it does not seem possible that nitrogen embolism could occur. The provision that the gas should always be under negative pressure at the beginning of the operation makes it impossible that it should be forced into a blood-vessel; if the trocar entered a vessel and were connected with the nitrogen, the apparatus would act as an aspirator: blood would appear in the little glass tube inserted between the trocar and the india-rubber tube. Still one has to be prepared for errors of technique. An awkward assistant may turn in the gas under positive pressure. Some unprevisive mistake may be made. Therefore I take a further caution which gives an absolute security: when I puncture a chest for the first time I always fill the apparatus with oxygen (46). Oxygen can be injected into the circulation without danger. I have made numerous experiments proving that, injected into the veins of a dog, it combines immediately with haemoglobin and is absorbed. Gaertner has made similar researches with the same result. Therefore if bad luck determined the introduction of the trocar into a vein, the pressure in the cylinder being positive, it would be absolutely harmless. After some 50 cubic centimetres have been injected into the pleural cavity, nitrogen can be safely substituted for oxygen in the apparatus. This same caution has been proposed also by Deneke (17). It is exceedingly simple to perform the substitution of one gas for another; and I do not think the time it requires exceeds two minutes.

With this modern puncture method Brauer's incision compares rather unfavourably. It requires the same aseptic precautions as any surgical operation in the chest, and therefore cannot easily be performed by a physician; the question of the deep sutures especially requires much attention. Brauer and Spengler quote a case of von Muralt's where wound-injection caused a rapidly fatal pyopneumothorax, whereas a puncture requires just the same aseptic precautions as a puncture for pleural effusions. If a first attempt with the trocar is unsuccessful—in other words, if adhesions obliterate the pleural space in the region chosen for puncturing—other attempts can be tried without delay in other places. But an unsuccessful incision will in all probability not be followed by a similar attempt before several days.

It is further noteworthy that the greater number of fatal embolic complications hitherto published have been observed in the course of the treatment, during or after a *refilling*, by physicians who, for the first injection, used the incision method. Brauer and Spengler each experienced one of those fatal cases. Weiss, who adheres to Brauer's views, quite recently published another one (65). The physicians who use the puncture method, with manometric readings, Saugman and Hansen, von Muralt, Dumarest, Küss, never had such an accident to deplore, although their statistics comprise a considerable number of cases. To speak with Forlanini, nitrogen embolism during a pneumothorax puncture belongs, or ought to belong, to the first historical period of the collapse therapy.

To conclude this argument, I shall say, in agreement with the majority of

authors, that the puncture method is the simplest and, I may add, safest technique for establishing a therapeutic pneumothorax, if it is practised with an instrument provided with a manometer and with a blunt trocar.

But the incision method deserves not to be entirely abandoned. Küss (35) keeps it in reserve for difficult cases, when several attempts to create a pneumothorax by simple puncture have been unsuccessful because of adhesions, although the physical examination suggests that there is a compressible lung. But in such cases Brauer's incision is not sufficient, in my opinion. It is more often advisable to resect a rib or two, in order to explore a larger area of pleura; if a place is found where the pleural space is not obliterated, one may liberate with a blunt instrument as many adhesions as possible, and so establish a partial pneumothorax. After careful suturing of the wound further injections under increasing positive pressure may destroy more adhesions and make the pneumothorax more complete. Dr. Lecène performed that operation for a patient of mine—under local novocaine anaesthesia—with a remarkably good result, more than a year ago: yet this method should be applied only to exceptional cases (46).

§ 6. *The Further Injections.*

The quantity of nitrogen which should be injected at first has been very much discussed. Brauer and Spengler give from half a litre to one litre; 'more', they say, 'is unnecessary; less than half a litre makes the refilling more difficult.' Forlanini injects generally 200 to 400 c.c. of gas the first time; exceptionally only—for instance, in cases of haemorrhage—does he give as much as 500 or 600 c.c. Saugman and Begtrup Hansen also prefer those small doses.

Subsequent injections, at short intervals, increase the collapse of the lung, which is never complete from the beginning. But the quantity of gas injected each time is much less important to consider than the measure of the intrapleural pressure obtained. If the first pneumothorax induced is a very partial one, limited by adhesions, the pressure will become positive after a small volume has been introduced, and themanometer will rise rapidly. If, on the contrary, the whole pleural space is free, several hundreds of cubic centimetres of nitrogen will be wanted to convert the negative pressure in the pleura into a pressure equal to atmospheric pressure or above it.

The pressure which obtains and maintains complete collapse of the lung varies very much from one patient to another. When there are no pleural adhesions, when there is little condensation of the lung, a slight positive pressure —2 to 4 cm. of water—is sufficient to keep the lung perfectly compressed. It would even be dangerous to increase the pressure; it would displace the mediastinum to a too considerable degree. On the other hand, when the lung remains attached to the chest by adhesions, one has to use increasing pressures in order to obtain collapse—up to 35 or 40 cm. of water. That this has to be done

cautiously it is hardly worth mentioning. One must always be prepared to withdraw a certain quantity of gas some hours after the refilling, if the patient complains of chest pains, of dyspnoea, or circulatory troubles. But, as a rule, one has very seldom to do so.

During a nitrogen injection it may happen that the pressure suddenly falls, to rise up again after a time: it is a sign that an adhesion has been ruptured. The available space in the pleural cavity has been increased, the gas expands, the pressure accordingly falls; usually the patient experiences a sharp pleural pain at the same time. This incident is never followed by any inconvenience; on the contrary, it must be considered as a favourable symptom, permanent adhesions being the greatest obstacle to the efficiency of pneumothorax therapy.

Once the maximum collapse of the lung has been obtained, the only object to be kept in view is to maintain permanently the pressure sufficient to produce this degree of collapse. During the initial period one has to refill very often —every second day, or twice a week, or every week. But after a certain time the pleura loses its capacity of absorbing nitrogen. The pressure keeps well, and it is enough to refill the pleural cavity with small quantities of gas every three, four, or six weeks.

Up to the last year Forlanini absolutely denied the advisability of measuring the pressure in the pleura. He considered the manometer as a useless, expensive, and disturbing apparatus, and maintained that with the fluoroscope and the classical methods of auscultation and percussion it was always possible to have an accurate idea of the condition of the compressed lung. He has since abandoned this position and added a manometer to his apparatus. But, as L. v. Muralt (40), to whom we owe very interesting manometric studies, wisely remarks, the pressure readings alone cannot inform us of the degree of lung collapse obtained. The manometer is indispensable. It is not sufficient. We want the constant control of the fluoroscope. To all physicians who have practised artificial pneumothorax, it has appeared evident that the classical stethacoustic methods—I mean percussion and auscultation—are not able to inform us always with accuracy of what is going on behind a pneumothorax. Whereas the Röntgen-rays are the most precise and faithful means of knowing the condition of the different parts of the lung, to what degree it is compressed and immobilized, how far the mediastinum and heart are displaced, the fluoroscope shows the exact size, form, and location of adhesions. It is easy to compare their degree of distension from one refilling to the following one, as well as to ascertain whether they have been ruptured or not. Liquid effusions in the pleural cavity, which often escape the most painstaking stethacoustic investigations, are easily discovered with the fluoroscope. As I have shown with Maingot (47), the necessity of a new nitrogen injection is best determined by an X-ray examination. The orthodiagraphic method enables us, namely, to measure exactly the size of the compressed lung; if its dimensions have increased, one can be certain that it begins to expand again. I have shown also that—when there are no diaphragmatic adhesions—the well-known Kienboeck's

phenomenon, inspiratory elevation of the diaphragm on the side of the pneumothorax, is due to a positive intrapleural pressure. In other words, when a fluoroscopic examination shows no Kienboeck's phenomenon, it means that the pressure in the pleural space is no longer positive, and that nitrogen must be injected again. It would carry us too far should I endeavour to give a detailed account of the asssitance which the collapse therapy gets from the Röntgen rays. This assistance is indispensable; it is the *sine qua non* of any rational and methodical collapse therapy. I believe the failure of many older attempts can be explained by the consideration that they were made before Röntgen's discovery.

§ 7. *Accidents, Difficulties, Complications.*

I have dealt already with the severest accident which can occur in the course of pneumothorax therapy, namely, nitrogen embolism in one of the cerebral arteries. It has proved fatal in some cases, and in some others has caused permanent hemiplegia. All the improvements in the technique of artificial pneumothorax were meant to exclude every possibility of cerebral embolism. This has been now achieved successfully, and we can repeat with Forlanini—who, by the way, was the last one to adopt those improvements—that cerebral embolism belongs to the historical period of pneumothorax therapy.

So-called pleural reflexes play an important part in the communications of some authors. Forlanini especially describes them very abundantly. They occur with almost immediate suddenness, generally just when the needle penetrates into the thorax, seldom after the injection has been performed. They may be characterized by delirium, loss of consciousness, convulsions, flaccid paralysis of the limbs, tachycardia, extremely weak action of the heart, cyanosis, irregularities of breathing, etc.

Brauer and Lucius Spengler suggest that in many cases those accidents were caused by nitrogen embolism. Nevertheless they do not deny—and, I think, no physician would deny—that there is such a thing as a pleural reflex; but they admit that it must be a very rare occurrence. Personally, they have observed a case of glottic spasm which they refer to a pleural reflex. Brauer also noticed pain in the side, with slight temporary syncopal tendency, in a patient whom he had injected with *cold* nitrogen. He insists accordingly on the necessity of warming the gas-containing cylinder to body's temperature. Yet, as Küss remarks, it is self-evident that nitrogen being a gas, having therefore a very low specific warmth, and being moreover slowly displaced through a relatively long india-rubber tube, it will, whatever the temperature of the gas-holder may be, acquire exactly the same temperature as the india-rubber tube.

The same syncopal tendency coincident with pleural pain has been observed by Weiss. Saugman and Hansen have never seen anything of the kind. Many authors who have considerable experience in pneumothorax therapy never

mention it. For my own part, I have never seen a single accident corresponding to Forlanini's description. Careful local anaesthesia with novocaine, and, in the case of a first injection, a previous subcutaneous dose of morphia, give an almost absolute security in this respect.

Pain, of course, is sometimes observed, especially in cases with adhesions, and when high positive pressures have been used. It sometimes appears only several hours after the injection; it is never of an alarming character.

Superficial emphysema can be avoided by temporary compression on the site of the puncture. It is frequently met with after Brauer's incision. It is a somewhat disagreeable but perfectly harmless incident.

Deep emphysema is more awkward. It is due to the penetration of gas into the subpleural connective tissue, or even into the interstitial tissue of the lung, through an error of technique. At first it gives no symptoms. But the gas, making its way through the mediastinum, ascends along the oesophagus and trachea, and finally—sometimes only after a day or two—appears in the form of subcutaneous emphysema of the cervical region. The pressure on the oesophagus can produce dysphagia, and the whole process occasions a good deal of discomfort and pain. However, it always subsides by itself, and never causes any serious accident.

If the heart has been displaced more than necessary, one might observe, some hours after the nitrogen injection, a certain degree of dyspnoea with palpitation, and cardiac anxiety. One might even be obliged to withdraw a certain quantity of gas. But this is a very rare occurrence, which the control of the fluoroscope and manometer enables us to avoid in almost every case.

Some transient digestive troubles may happen after each refilling, when the pneumothorax is on the left side. They are due to compression of the stomach.

Pleuritic effusions are a very common incident in the course of the treatment. They are mentioned by all authors. A. Weiss (65) is quite right, in my opinion, when he estimates that they are met with in about fifty per cent. of cases. They may appear without any symptoms, and be fortuitously discovered by fluoroscopic examination. They may be very little abundant, last a week or two, or even more, and disappear. But it also happens that they are accompanied with fever and last several months. The effusion is always serous, seldom blood-containing. Its transformation into empyema, noticed by Dumarest (18), is quite exceptional. The origin of these serous exudates has been the cause of much discussion; that they should be caused by some irritant action of nitrogen, as some authors have supposed, is quite out of the question, as they never complicate experimental pneumothorax. Brauer and Wellmann think that their production is favoured by high intrapleural pressure; Keller (32), that high pressure prevents them. Saugman supposes that the stretching and rupturing of adhesions might help to their production. Weiss considers that all those exudates are of infectious origin. As a matter of fact, the presence in them of tubercle bacilli can almost always be proved by inoculation of guinea-pigs. Lymphocytes are generally found in abundance in the liquid. But I have

noticed in several cases a remarkable number of eosinophils and mast cells, sometimes associated with the presence of an unusual number of those white cells in the circulating blood.

In the greater majority of cases effusions must not be considered as complications. They contribute to the compression of the lung, and if they do not cause too great a displacement of the mediastinal organs it is not advisable to tap them. They generally cause an increase of the intrapleural pressure, so much so that it is sometimes necessary to withdraw a certain amount of nitrogen. Injections of nitrogen have commonly to be repeated at much longer intervals when there is a pleural effusion.

Purulent pleural effusions are a much more awkward complication. They may be due to some intercurrent infection, appearing as a sequel of a tonsillitis, for instance ; or they are a consequence of a spontaneous perforation of the lung. Forlanini (25) has observed this fatal accident in eight out of his 139 cases. It always occurred during the period of clinical healing, which, as the Italian author remarks, is generally not coincident with anatomical healing. The patients—seven men and only one woman—were all leading an incautious life, escaped more or less the physician's supervision, and refused to avoid physical strain. It is interesting to note that other authors are remarkably silent on the subject of perforation.

The greatest difficulties in pneumothorax therapy are caused by pleural adhesions. If they are extended, causing a real symphysis, they absolutely preclude the possibility of establishing a pneumothorax. If they are only partial, if there is sufficient free pleural space to allow the injection of a certain amount of gas, the treatment can be attempted. Not only is it sometimes a not altogether impossible task gradually to increase the volume of the pneumothorax, to loosen, dislocate and rupture the adhesions ; but one is often surprised to see what a real benefit certain patients can derive from an only partial pneumothorax. It is not possible to foresee with an absolute certainty what the condition of the pleural space really is. The physical signs, even the fluoroscopic examination, give us nothing more than probable information in this respect. To find a free pleural space where an efficient pneumothorax can be established in cases where it seemed that a symphyseal adhesion was certain, is not a rare occurrence. And one has sometimes the deception of finding absolutely blocked a pleural space which one had every good reason to suppose free.

That the patient should have a certain amount of sound-mindedness and stability of character is a necessary requirement in many medical circumstances. It is never more so than when the physician intends to attempt pneumothorax therapy. A persevering, patient, and intelligent co-operation on the part of the patient is a very important condition of success. If this is not to be had, one should give it up.

§ 8. *Selection of Cases for Collapse Therapy.*

Hitherto the greater number of patients treated with artificial pneumothorax were affected with severe pulmonary tuberculosis, characterized by advanced, extended, destructive lesions—mostly cavities—a marked tendency to aggravation, and, generally, persistent fever.

Of course the lesions were one-sided as a rule. But Forlanini, Brauer, Saugman, and the majority of authors insist that one should not be too punctilious as regards unilaterality. A slight affection of the opposite lung is often very fortunately influenced by the pneumothorax on the other side, although these cases evidently require quite a special amount of caution and care. It cannot be denied, however, that torpid lesions in the so-called healthy lung may be activated to a degree which enforces abandonment of the collapse therapy. But it is an exceptional occurrence. To be aware of the danger is also to be able to prevent it.

Moreover, Forlanini, in his last extensive publication (25), reports several cases where pneumothorax improved in a very conclusive way the condition of the opposite lung. In one of them (Case No. 9 of his statistics) death, caused by a non-tuberculous disease, occurred thirteen years after the establishment of a right-sided pneumothorax ; during the course of treatment the patient had shown for some time symptoms of a tuberculous lesion in the left supra-clavicular region. The post-mortem gave evidence of a pleuro-pulmonary sclerosis of the left apex, the cicatricial sequel of the healed tuberculous focus. Forlanini also reports two cases (Nos. 65 and 122) which he decided not to treat by artificial pneumothorax because they were bilateral. Subsequently spontaneous pneumothorax occurred. He then entertained the gas collection by injections of nitrogen, and was surprised to observe a favourable evolution of the lesions in the opposite lung as well as in the collapsed one. One of these cases, which he followed for three years, is now on the way to complete clinical recovery.

Acute miliary tuberculosis is, of course, excluded from collapse therapy. So is pulmonary tuberculosis coincident with intestinal tuberculosis. The coexistence of tuberculosis of the larynx should not be an absolute contra-indication, according to Da Gradi (16) and to J. Courmont (14) who saw a favourable evolution in some cases. The same can be said of chronic nephritis, according to Forlanini and Wellmann (66). But amyloid degeneration of the kidneys or of any organ should be an absolute contra-indication.

Lung haemorrhage, far from excluding artificial pneumothorax, is, on the contrary, an urgent indication. The collapse of the lung is often the only way to stop haemoptysis. Pleural effusion, especially when the lung is notoriously tuberculous, offers an excellent opportunity for initiating artificial pneumothorax.

Forlanini considers that acute tuberculous hepatizations, and caseous pneumonias are not amenable to collapse therapy; but Brauer and Saugman are of a different opinion. They have had good results in such cases, which I can confirm from my own experience.

The great number of admirable recoveries obtained in advanced cases raises, of course, the question whether more initial forms ought not to be submitted also to pneumothorax therapy. In reading Lemke's paper, one is struck by the fact that he treated a great number of cases where the lesions were not of an ulcerative character and had a limited extension, cases which to-day would certainly not be considered fit for pneumothorax therapy, according to the now classical indications. These cases did very well and had no more bacilli in their sputum after a surprisingly short duration of the collapse. If pneumothorax treatment should prove shorter and more efficacious than sanatorium treatment in such cases, it should certainly be preferred. There is no doubt that the indications for pneumothorax therapy will become broader than they are nowadays. But every physician can feel how cautious one must be on that line, and how dangerous it could be to give pneumothorax as a kind of universal treatment for tuberculosis of the lung.

I must add that tuberculosis is not at all the only morbid alteration of the lung which artificial pneumothorax can improve. Bronchiectasis, gangrenous cavities, chronic pneumonias, and several chronic, limited, suppurative diseases of the lung can be successfully treated by pneumothorax.

§ 9. *Clinical Results and Duration of Treatment.*

It is, for the present, absolutely impossible to give a statistical account of the results obtained so far with pneumothorax therapy. Not only does the selection of patients vary very much from one author to another, not only is there a similar variety in the perseverance with which the treatment is continued, but the criterions of improvement or recovery are exceedingly different. My intention, when I began writing this paper, was to put together in a single table all the cases hitherto published, and to give percentage figures of the successes, failures, and accidents. I soon realized that this was a hopeless scheme. The reasons are obvious; so much so that the majority of authors have simply published the histories of their cases without even attempting to give a statistical *résumé* of them.

To judge fairly of the value of the new method, it is necessary to keep in mind two points:

1. Fatal accidents caused by artificial pneumothorax are a thing of the past, and the memory of disastrous occurrences caused by a bad technique ought not to deter us from a method which is now absolutely innocuous.

Not a single example of embolism or of fatal syncope is mentioned in the most extensive collections of histories recently published: I may quote the papers of Wellmann (27 cases) (66), of Keller (40 cases) (32), of Saugman and Begtrup Hansen (33 cases) (53), of Mary Lapham (15 cases) (36), of Samuel Robinson and Cleaveland Floyd (28 cases) (48), of H. Brauns (98 cases) (6), of Dumarest (27 cases) (19).

2. If the attempt to create an artificial pneumothorax is a partial or complete failure, the condition of the patient remains unchanged. The operation in itself—and more especially so the puncture method—is absolutely harmless. If adhesions are met, which are an obstacle to the introduction of nitrogen, or if only a small limited, unefficacious pneumothorax is obtained, the patient is none the worse for it: simply, collapse therapy must be abandoned.

Now let us consider the ordinary effect of more or less complete artificial pneumothorax on the type of patients which are more commonly treated with the collapse-method, namely, cases of extended one-sided tuberculous infiltration of the lung with cavity, abundant expectoration, and fever. The results are precisely what one would theoretically expect: the amount of expectoration diminishes gradually—sometimes very rapidly—to an extraordinary degree, and, at the same time, the temperature is reduced to normal; coughing subsides; the appetite comes back; all the painful and disagreeable subjective sensations caused by fever and intoxication disappear. Patients who previously were confined to bed are able to walk, to talk, to read, and, sooner or later, to work.

The degree of improvement obtained is proportioned to the amount of collapse established. If the nitrogen is allowed to get partly absorbed, and if consequently the intrapleural pressure falls down under its optimal height—which varies according to the patient—coughing and expectoration become more abundant again, fever and malaise come back. It is therefore absolutely necessary to keep the intrapleural pressure to a constant level. But this, with the control of frequent fluoroscopic examinations, and provided the patient has some good will and common sense, is a relatively easy task. In many cases, the patient can be allowed to live in his home, to resume his work, under the condition of coming once every fortnight or every third week to the physician for a nitrogen injection.

There are few therapeutic results more striking and more gratifying for the physician than the complete transformation caused in a tuberculous patient's life by a successful artificial pneumothorax. In a great number of cases one is entitled to speak of real clinical recovery.

But the problem is not definitely solved when all morbid symptoms have disappeared in the compressed lung, when cough, expectoration, and fever have subsided, even when tubercle bacilli are no more to be found in the sputum. When this condition of restored health has lasted for a certain time, one must try to put an end to compression and collapse, to let the nitrogen be gradually resorbed and the re-expanded lung resume its respiratory function. To decide when this should be done, in other words when the treatment should be concluded, is an exceedingly delicate matter. Evidently one ought not to let the lung re-expand before having good reasons to believe that there is not only a clinical but also an anatomical recovery of the tuberculous lesions. No absolute sign can inform us of that. The later the better is a formula to which all authors seem to adhere. Forlanini expresses the opinion that one should in no case wait less than one or two years, and that the treatment will very

often have to be prolonged much longer. That the end of the treatment should only consist in abstention from new gas injections, not in withdrawal of nitrogen, is self-evident. Of course, the patient must be followed very closely during this period, and compression should be renewed at the first sign of activation of old lesions. Only when the patient remains in good health after the nitrogen has been entirely resorbed can one speak of real, complete recovery. That such recoveries can be achieved there are numerous examples in the literature of pneumothorax. Nothing can be more suggestive than to read the extensive case-histories describing them in the various publications I have quoted above. To give an idea of their amount and value I shall limit myself to the exposition of results obtained by L. Brauer and Lucius Spengler. These two physicians, working conjointly, published in 1911 the complete histories of the 102 cases (5) treated by them during the five foregoing years. Out of those 102 histories, L. Spengler, in a special publication (58), has selected the cases where, after clinical recovery had been achieved through compression, the nitrogen had been allowed to resorb and where consequently the pneumothorax had been put to an end for at least nine months—excluding all the cases where pneumothorax was still existent, however striking their clinical recovery may have been. The cases thus selected were *fifteen* in number. They were all severe cases, with fever, abundant bacilli in the sputum—cavities were evident in eight of them. At the time of Spengler's publication they were all for more than a year without fever, without expectoration, and fully able to work. Of twelve among them the sputum has been examined and was found free from bacilli. A more complete recovery cannot be imagined, and one must confess that no other dietetic, hygienic, or therapeutic treatment can achieve success of that kind.

What is the functional value of the re-expanded lung? It sometimes seems to be impaired, and it even happens that the lung can never again enter in contact with the chest wall, a certain amount of gas remaining permanently in the pleural space. Forlanini mentions such a case. But he quotes two other cases where, for some reason, he had to establish a pneumothorax on the hitherto healthy side, and where the re-expanded lung was perfectly equal to its task. In one of his cases the compression had lasted eight years (25). This evidently contradicts the anatomical and experimental researches which point to a sclerotic degeneration of the healthy compressed lung. But even Forlanini considers the above-quoted case as rather exceptional. In the majority of patients the once collapsed lung remains small and atrophied. The chest wall is deformed as after pleurisy. The visceral and parietal pleurae adhere to each other, establishing a more or less complete symphysis. In other words, the tuberculous lung after it has recovered through artificial pneumothorax is a cicatricial lung. That it may, however, be up to its function to a more or less satisfactory degree is obvious.

§ 10. *Morbid Anatomy.*

For the right understanding of the therapeutic effects of artificial pneumothorax, nothing seems more important than the study of the anatomical changes which occur in the tuberculous lung under the influence of prolonged compression. Systematic investigations in that direction are far from being numerous in the literature, and many an important question is still waiting for an answer. It must be considered also that among the few post-mortems published the majority are those of bad cases, not favourably influenced by pneumothorax therapy. Such are Graetz's (28) three autopsies, made respectively six months, seven weeks, and six weeks after nitrogen had been for the first time introduced into the patient's pleural space. Such is Warnecke's case (five months) (64); such also is Kistler's (nine months) (33). The short duration of life after the lung collapse had been induced in these cases shows that the treatment had hardly modified their natural evolution towards death. In Forlanini's last monograph, on the contrary, we find some information on post-mortems made several years after the pneumothorax had been established, in cases where the lesions of the compressed lung seem to have been brought to the point of absolute standstill.

We need not deal at any length with the macroscopical changes in artificial pneumothorax: the retracted and atelectatic lung, the pleural adhesions, the displacement of the heart and mediastinum. There is nothing in this picture which differs essentially from the classical description of spontaneous pneumothorax. But the microscopical study of the compressed lung is of much more concern to us.

A marked tendency to over-production of fibrous tissue in all tuberculous lesions of the atelectatic lung is the characteristic fact emphasized by every author. This hypertrophied fibrous tissue is to be found abundantly along and around blood-vessels and bronchi, representing, as it seems, the healing process of perivascular and peribronchial inflammation. Pneumonic foci and old isolated caseous tubercles show a remarkable cicatricial transformation and are surrounded by fibrous tissue. The liquid component of the caseous masses is pressed out by the elastic retraction of the lung and evacuated through the bronchi; the rest is compressed more and more by the connective proliferation, and finally completely isolated in a coat of compact lamellous conjunctive tissue. The caseous substance dries up and often gets calcified. Cavities, if they are situated in a portion where compression has been more or less completely realized, can be entirely obliterated, their opposed walls having been brought in contact and having adhered to each other. According to Forlanini, who recently published an admirable microphotograph of such a case, the place of the cavity is taken by a scar, an irregularly shaped mass of dense fibrous tissue isolated in the midst of the lung parenchyma and having no connexion whatever with vessels or bronchi.

The fibrous tissue also forms thick subpleural layers, from which septa

penetrate the lung tissue in a centripetal direction. The interlobar pleurae are also thickened and may be adherent.

Warnecke, describing this condition, speaks of 'connective degeneration' ('bindegewebige Entartung') of the lung tissue, and compares it to diffuse, chronic induration, or to cirrhosis of the lung. Of course, one can easily object that similar processes are often observed to occur spontaneously in tuberculous lungs. But this objection does not hold good: in the post-mortems hitherto published, the intense fibrous proliferation was limited to the compressed lung; the other lung, affected with a progressive, fatal tuberculosis, presented no tendency at all towards fibrous degeneration.

That there is a causal relation between compression of the lung and fibrous proliferation seems indeed indisputable, although the real nature of this relation is still very obscure. Following Brauer's suggestion that the curative process in pneumothorax was probably dependent on a lymph stasis in the compressed lung, Graetz, Beneke Warnecke and Kistler admit that the proliferation of the connective tissue represents a reaction to a local irritation by tuberculous toxins which the blocked lymphatic vessels are unable to eliminate. Warnecke saw the lymph vessels enlarged on his sections, and so did Kistler. Another argument in favour of lymph stasis would be the abundant amount of anthracosis in the compressed lung. According to Warnecke, coal pigment accumulates near the bronchi, around the blood and lymph vessels, on the periphery of fresh and older caseous foci, in the interstitial septa of the compressed but still air-containing alveoli. In the other lung, anthracosis is much less pronounced.

That lymphatic stasis alone—without any co-operation of tuberculous toxins—should be able to cause fibroid degeneration of the lung seems at first unlikely. And yet Kaufman (31) found the same proliferation of the connective tissue of the lung, with fibrous thickening of the pleura, in a healthy, non-tuberculous dog on which he had performed a left-sided pneumothorax and maintained it during ten months. The experiment seems to have been very carefully conducted. O. Bruns (7) had obtained similar results with rabbits and goats. Burckhardt (9) found the same fibrous lesions in the otherwise healthy inferior lobe of a lung in a patient whom he had treated with artificial pneumothorax for tuberculosis of the upper lobe. Weiss (65) reports two similar observations and expresses some doubts as to the re-expanding capacities of such lungs.

Together with the hypertrophy of the connective tissue one notices a transformation of the respiratory epithelium and a narrowing or obliteration of the bronchi and bronchioli. The alveoli are reduced to little round, glandular-looking bodies, the alveolar epithelium having returned to its foetal cubical shape. Similar productions have been found in chronic inflammations of the lung, and more especially in indurative forms of lung tuberculosis. In compressed lungs they are met with only in the immediate neighbourhood of hypertrophied connective tissue. Portions with more or less normal alveoli are always to be found even in atelectatic lobes. In other places rows of epithelial cells are severed from their connexions and surrounded by thick bundles of

connective fibres. This means, of course, a dislocation of the normal alveolar tissue by the fibrous proliferation; in other words, it is a destructive process. But it seems very difficult, as remarked by Kistler, to make out whether this destructive process is limited to previously diseased alveoli, or more or less generalized.

It is a very striking fact that no fresh tubercles are to be found in the compressed lungs. All the authors agree on that point. The post-mortems published so far concern cases where death was the result of progressive ulcerative tuberculosis in the other lung or of miliary tuberculosis. Not a single fresh tubercle could be discovered in the pneumothorax lung. The same remark has been made many years ago by the writers who observed the beneficial influence of spontaneous pneumothorax. 'One must admit', says Forlanini, 'that the collapse treatment is an obstacle to any further development of tubercles.'

§ 11. *Theoretical Explanation of the Therapeutic Effects of Pneumothorax.*

How can one account for the beneficial effect of compression of the lung in tuberculosis? It seems, at first view, that the simple mechanical explanations of Potain or Murphy—not to speak of Carson—were self-evident and rational. Still, the temptation is great to look behind the curtain of mechanical facts and to try and catch something of the more mysterious cellular or humoral processes which they determine. Many conflicting theories—some of them very strange—have been proposed.

We need not give great importance to the views of Daus (15), who thinks that pneumothorax favours the production of the fibrogenous toxin of Koch's bacillus, at the same time preventing the formation of the caseogenous toxin. The production of fibrous tissue in the compressed lung is indeed, as pathological findings show, the most striking result of a long-standing pneumothorax. But the real nature of the fibrogenetic process seems to be exceedingly obscure. Kaufman admits that it originates spontaneously in the *healthy* collapsed lung, and so does Bruns. They have both experimented on a very small number of animals, and their researches ought certainly to be repeated. But if their findings are confirmed, one should be led to conclude that the proliferation of fibrous tissue which arrests the evolution of tuberculous lesions in the collapsed lung is absolutely independent of the tuberculous process itself; in other words, that it is totally different from the fibrogenesis which plays such an important part in the spontaneous healing of phthisis.

This raises another question: Does artificial pneumothorax produce anaemia of the lung or, on the contrary, hyperaemia? Sackur (50) and, more recently, Sauerbruch (51) consider that pneumothorax produces a hyperaemia, that it acts like Bier's passive congestion. Poiseuille (43) in 1855 thought that the lung is better irrigated during collapse than during inspiratory expansion. Quincke

and Pfeiffer (45) supported this theory, in favour of which Cloetta (13) has recently contributed the evidence of his plethysmographic experiments. Meyerstein (40) remarks that if this be true of the collapsed lung, it is not so of the compressed lung. Bruns, by comparing the quantity of blood contained in both lungs in cases of unilateral experimental pneumothorax, found that even in the simply collapsed lung there is not hyperaemia but anaemia. The anaemic theory is supported by Graetz, by Heisler and Tomor (29), by Brauer and his school. That anaemia plays an important part in the therapeutic effect of pneumothorax was, in former days, the opinion of Adams and of Potain.

Whether the result of artificial pneumothorax be hyperaemia or anaemia of the lung should be practically unimportant, as both conditions, according to certain experimental researches, can produce sclerotic changes in the lung. Bruns (8) claims to have been able to determine fibrosis of the lung by ligating one of the pulmonary *arteries*; the over-production of connective tissue should be the direct consequence of ischaemia. But, on the other hand, there are experiments by Tiegel (62) which are supposed to prove that partial or total ligation of a pulmonary *vein* should have the same result as ligation of the artery.

One must confess that theories of the curative effect of pneumothorax based on circulatory changes are not very satisfactory. Brauer considers that lymph stasis, due to immobilization of the lung, is a much more important factor. That there is lymph stasis in a compressed lung is proved by post-mortem evidence (Graetz, Kistler, Warnecke) and by experiments (Shingu, 61). Its consequences, according to Brauer, are not only lessened resorption of toxins and resultant improvement of the general condition, but also local irritation producing fibroid hyperplasia. Some of Brauer's followers even consider that the constantly high opsonic index observed in patients treated with pneumothorax by Pigger (42) speaks in favour of this lymphatic stasis theory. This seems rather too far-fetched.

Forlanini (27) has a very original conception of the part played by pneumothorax in the healing of phthisis. He admits that the caseous necrosis of the primitive tuberculous lesions of the lung is not due to the specific properties of the bacillus, but essentially connected with the respiratory movements of the lung, which produce a progressive diminution of blood and lymph irrigation of the tuberculous tissue, leading to its absolute ischaemia and finally to its destruction. 'If the lung', such are his words, 'were a normally unmovable organ, it could not be affected with phthisis.' Therefore complete immobilization of the tuberculous lung must evidently arrest the phthisical process by impeding the ischaemia due to respiratory movements.

I must confess that the simple mechanical explanation, as it has been outlined by Murphy (see above, p. 263), seems to me more satisfactory than the more or less obscure hypotheses just alluded to. It is perfectly intelligible that the physiological movements of the lung, the constant distension of its tissue, the 'interminable contest' which Carson described between the elasticity of the

organ tending to reduce it to its foetal volume, and the action of the chest muscles tending to its utmost dilatation, should be in the way of any natural process of cicatrization. Collapse or compression immobilize the lung; they suppress all the mechanical obstacles which prevent cicatrization. They allow the natural tendency to healing to have its own way; they give it a chance. It is an old experience that tuberculosis of a knee or hip joint will not heal if the joint is not immobilized, that a lupus located on a mouth corner is incurable. A successful pneumothorax puts the tuberculous lung in a condition similar to a carefully immobilized tuberculous knee-joint. So far the action of pneumothorax may be considered as emphatically negative. It does away with the most powerful obstacle to spontaneous cure. It creates nothing. It has no positive influence over the virulence or vitality of the tubercle bacilli. The healing in itself is due to a process of acquired immunity, the exact nature of which is still extremely obscure. But it does not seem wise to confuse this process with the mechanical action of pneumothorax. The aim, in pneumothorax therapy, should not be to favour the acquisition of immunity, to influence more or less mysterious cellular or humoral conditions, but to produce a collapse and an immobilization of the lung as perfect and as effective as possible.

In concluding this critical review, I must acknowledge that many an important aspect of the subject has been left without even mention. The question of artificial pneumothorax is a very complex one, and the amount of practical and theoretical research which it has inspired during the last few years is overwhelming. I felt obliged to confine myself to its historical and properly therapeutic side. Even within those narrow limits I could not possibly be complete. It would have been particularly advisable to dwell on the other surgical methods which are at our disposal to achieve compression of the lung. Collapse therapy is evidently the best and, in the present state of things, the only effective treatment we can oppose to progressive phthisis. Unfortunately, one has to give it up in many cases where all the other conditions seem favourable to its use, because of extensive pleural adhesions. Here, it seems, surgical methods should come to help. Some very interesting attempts have been made in that direction. But this is another story.

REFERENCES.

The references given in this paper are far from representing a complete bibliography of the question of artificial pneumothorax. A very full list of the publications on the subject has been given by L. Brauer and L. Spengler in *Beiträge zur Klinik der Tuberkulose*, vol. xiv, p. 464, and vol. xix, p. 333. The latest additions to this list will be found in *Internationales Centralblatt für die gesamte Tuberkulose-Forschung*, 6th year, no. 9, p. 479 (July 31, 1912), and 7th year, no. 1, p. 1 (Nov. 30, 1912). An extensive bibliography will also be found in Carlo Forlanini's important paper, 'Die Behandlung der Lungenschwindsucht mit dem künstlichen Pneumothorax,' in *Ergebnisse der inneren Medizin und Kinderheilkunde*, vol. ix (1912), p. 622, and in the *Rivista delle pubblicazioni sul pneumotorace terapeutico*, a periodical published by Forlanini in Pavia.

1. Adams, 'The Surgical Treatment of Pulmonary Cavities,' *Lancet*, April, 1887.

2. L. Brauer, 'Die Behandlung der einseitigen Lungenphthisis mit künstlichem Pneumothorax (nach Murphy).' Aerztl. Ver. zu Marburg, Sitzb. vom 20. xii. 05 ; Offiz. Protok. in *Münch. med. Wochenschr.*, 1906, 337.

3. L. Brauer, 'Der therapeutische Pneumothorax,' *Deutsche mediz. Wochenschr.*, 1906, 652–7.

4. L. Brauer und Lucius Spengler, 'Erfahrungen und Ueberlegungen zur Lungenkollapstherapie. Die Technik des künstlichen Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xiv, Heft 4, 419–76.

5. L. Brauer und Lucius Spengler, 'Klinische Beobachtungen bei künstlichem Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xix, Heft 1, 1–335.

6. H. Brauns, 'Meine Erfahrungen mit der Forlanini'schen Stich-Methode in der künstlichen Pneumothoraxtherapie,' *Zeitschrift für Tuberkulose*, xviii, Heft 6, 549–60.

7. O. Bruns, 'Ueber Folgezustände des einseitigen Pneumothorax,' *Brauer's Beitr. z. Klin. der Tuberkulose*, xii, Heft 1, 1–57.

8. O. Bruns, 'Ausschaltung einzelner Lungenlappen zu therapeutischen Zwecken,' *Deutsche mediz. Wochenschr.*, 1911.

9. O. Burckhardt, 'Eine Lunge von einem Patienten, der mit künstlichem Pneumothorax behandelt worden war,' *Med. Gesellsch. Basel*, Feb. 16, 1911.

10. James Carson, 'On the Elasticity of the Lungs,' communicated by Thomas Young, M.D., read Nov. 25, 1819 (*Philosophical Transact. of the Royal Society of London, for the year MDCCCXX*, part i, 29–44).

11. James Carson, M.D., 'On Lesions of the Lung,' in *Essays Physiological and Practical*, printed by F. B. Wright of Castle St., Liverpool, 1822. This second paper I have not been able to procure. Piéry and Roshem give an account of it in their interesting paper, 'Deux précurseurs de Forlanini,' *Lyon médical*, Jan. 15, 1911.

12. Cayley, 'Notes of a Case of Haemoptysis treated by the Induction of Pneumothorax, so as to collapse the Lung' *Transact. Clin. Soc. Lond.*, 1884–5, xviii, 278–84 ; *Brit. Med. Journ.*, 1885, i. 991 ; *Lancet*, Lond., 1885, i. 894.

13. Cloetta, 'Ueber die Zirkulation in der Lunge und deren Beeinflussung durch Ueber- und Unterdruck,' *Arch. f. experim. Pathol. u. Pharm.*, 1911, lxvi. 409.

14. J. Courmont, 'Le traitement de la tuberculose pulmonaire par le pneumothorax artificiel,' *Lyon médical*, 1910, no. 50.

15. Daus, 'Historisches und Kritisches über künstlichen Pneumothorax bei Lungenschwindsucht,' *Therapie der Gegenwart*, May, 1909.

16. Da Gradi, 'Ueber den Verlauf der Kehlkopftuberkulose bei der mit künstlichem Pneumothorax behandelten Lungenschwindsucht,' *Deutsche mediz. Wochenschr.*, 1910.

17. Deneke, 'Künstlicher Pneumothorax,' *Deutsche mediz. Wochenschr.*, 1911.

18. F. Dumarest, 'Le Pneumothorax thérapeutique, la conduite de la cure, ses complications, ses résultats,' *Le Journal médical français*, 1912, 249–60.

19. F. Dumarest, 'Sur la pratique du pneumothorax thérapeutique. Statistique et résultats,' *La Province médicale*, 1910, 469–72.

20. Forlanini, 'A contribuzione della terapia chirurgica della tisi. Ablazione del polmone? Pneumotorace artificiale?' *Gazz. degli Ospedali*, 1882.

21. C. Forlanini, 'Contribuzione alla terapia dell' empiema pleurico,' *Il Policlinico*, 1890.

22. C. Forlanini, 'Primi tentativi di pneumotorace artificiale nella tisi polmonare,' *Gazz. med. di Torino*, 1894.

23. C. Forlanini, 'Primo caso di tisi polmonare avanzata curato felicemente col pneumotorace artificiale,' *Gazz. med. di Torino*, 1895.

24. C. Forlanini, 'Zur Behandlung der Lungenschwindsucht durch künstlich erzeugten Pneumothorax,' *Deutsche mediz. Wochenschr.*, 1906, 1401-5.

25. C. Forlanini, 'Die Behandlung der Lungenschwindsucht mit dem künstlichen Pneumothorax,' *Ergebnisse der inneren Medizin und Kinderheilkunde*, ix. 621-752.

26. C. Forlanini, 'Ueber den künstlichen, nachträglich doppelseitigen Pneumothorax,' *Deutsche mediz. Wochenschr.*, 1911.

27. C. Forlanini, 'Die Behandlung der Lungenschwindsucht mit dem künstlichen Pneumothorax', *Ergeb. der inn. Mediz. u. Kinderheilk.*, ix. 621-752.

28. Fr. Graetz, 'Der Einfluss des künstlichen Pneumothorax auf die tuberkulöse Lunge,' *Brauer's Beitr. z. Klin. der Tub.*, x, Heft 3, 249-78.

29. Heisler und Tomor, 'Altes und Neues zur Behandlung der tuberkulösen Haemoptoë,' *Münch. mediz. Wochenschr.*, 1910, 907-11.

30. Hérard, 'De l'influence favorable de l'hydropneumothorax sur la marche de la tuberculisation pulmonaire' (*Associat. franç. pour l'avancement des sciences*, 10e Session, Alger, 1881, Paris, 4 rue Ant. Dubois, 1882).

31. K. Kaufman, 'Ueber die Veränderungen der Pleura und Lungen gesunder Hunde durch künstlichen Pneumothorax,' *Brauer's Beitr. z. Klin. der Tuberkulose*, xxiii, Heft 1, 57-61.

32. Keller, 'Erfahrungen über den künstlichen Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xxii, Heft 2, 165-242.

33. E. Kistler, 'Beitrag zur pathologischen Anatomie des künstlichen Pneumothorax,' *Brauer's Beitr. z. Klin. der Tub.*, xix, Heft 3, 459-67.

34. G. Küss, 'La technique et les résultats immédiats du pneumothorax artificiel dans les formes avancées unilatérales de la tuberculose pulmonaire,' *Bull. et Mém. de la Soc. méd. des hôpitaux de Paris*, 1910, ii. 88-97.

35. G. Küss, 'Technique opératoire du pneumothorax artificiel,' *Le Journal médical français*, 1912, 229-36.

36. Mary E. Lapham, 'The Treatment of Pulmonary Tuberculosis by Compression of the Lung,' *The Americ. Journ. of the Med. Sc.*, cxliii. 503-17.

37. A. F. Lemke, 'Report of cases of pulmonary tuberculosis treated with intrapleural injections of nitrogen, with a consideration of the pathology of compression of a tuberculous lung' (50th Annual Meeting of Americ. Med. Associat., Columbus, Ohio, June 6-9, 1889), *Journ. of the Americ. Med. Associat.*, 1899, xxxiii. 959-63, 1023-7, 1077-84.

38. Meyerstein, 'Experimentelle Untersuchungen über die Resorption und Exsudation bei künstlichem Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xxiv, Heft 1, 19-54.

39. L. von Muralt, 'Die Behandlung schwerer einseitiger Lungentuberkulose mit künstlichem Pneumothorax,' *Münch. mediz. Wochenschr.*, 1910.

40. L. v. Muralt, 'Manometrische Beobachtungen bei der Ausübung der Therapie des künstlichen Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xviii, Heft 3, 357-84.

41. J. B. Murphy, 'Surgery of the Lung,' *Journ. of the American Med. Associat.*, 1898, xxxi. 151, 208-16, 281-97.

42. H. Pigger, 'Künstlicher Pneumothorax und opsonischer Index,' *Beitr. z. Klin. der Tuberkulose*, viii, Heft 4, 337-56.

43. Poiseuille, 'Recherches sur la respiration,' *C. R. de l'Acad. des Sciences*, 1855, 41.

44. Potain, 'Des injections intra-pleurales d'air stérilisé dans le traitement des épanchements pleuraux consécutifs au pneumothorax,' *Bull. de l'Acad. de Méd.*, 24 avril 1888.

45. Quincke u. Pfeiffer, 'Ueber den Blutstrom in den Lungen,' *Arch. f. Anat. u. Physiol.*, 1871.

46. E. Rist, 'Notes sur le pneumothorax artificiel,' *Le Journal médical français*, 1912, 237-9.

47. E. Rist and Maingot, 'Examen radiologique et pneumothorax thérapeutique,' *Bulletins et Mémoires de la Soc. méd. des Hôpit. de Paris*, 1912.

48. S. Robinson and Cleaveland Floyd, 'Artificial Pneumothorax as a Treatment of Pulmonary Tuberculosis,' *The Arch. of Internal Medicine*, ix. 452–83.

49. Rühle, in *Handbuch der speziellen Pathologie und Therapie von Ziemssen*, v, 3. Teil, 126.

50. Sackur, 'Zur Lehre vom Pneumothorax,' *Zeitschr. f. klin. Mediz.*, 1896, xxix. 25.

51. Sauerbruch, 'Zur Pathologie des offenen Pneumothorax,' *Mitt. a. den Grenzgeb. der Mediz. u. Chir.*, 1904, xiii. 399.

52. Chr. Saugman, 'Eine verbesserte Nadel zur Pneumothoraxbildung,' *Zeitschr. f. Tuberkulose*, xiv, Heft 2.

53. Chr. Saugman and Begtrup Hansen, 'Klinische Erfahrungen über die Behandlung der Lungentuberkulose mittels künstlicher Pneumothoraxbildung,' *Beitr. zur Klin. der Tuberkulose*, xv, Heft 3, 303–455.

54. Schell, 'A New Use of Dr. J. B. Murphy's Method of Immobilizing the Lung,' *New York Med. Journ.*, lxviii, 1898, Letter to the editor.

55. A. Schmidt, 'Zur Behandlung der Lungenphthise mit künstlichem Pneumothorax,' *Deutsche mediz. Wochenschr.*, 1906.

56. Späth, 'Ueber die Beziehungen der Lungenkompression zur Tuberkulose,' *Korresp.-Bl. des Württemb. ärztl. Landesver.*, 1888.

57. Lucius Spengler, 'Ueber mehrere Fälle von geheiltem tuberkulösen Pneumothorax, verbunden mit gleichzeitiger Heilung in vier Fällen,' *Zeitschrift f. Tuberkulose*, 1901, ii. 111.

58. Lucius Spengler, 'Dauererfolge bei Behandlung schwerer einseitiger Lungentuberkulose mittelst künstlichem Pneumothorax,' *Münch. mediz. Wochenschr.*, 1911, 460–2.

59. William Stokes, *A Treatise on the Diagnosis and Treatment of the Diseases of the Chest*, part i, Dublin, MDCCCXXXVII, 531.

60. *Dublin Journal of Med. Science*, v (quoted by Stokes).

61. Suzuo Shingu, 'Beiträge zur Physiologie des künstlichen Pneumothorax und seiner Wirkung auf die Lungentuberkulose,' *Beitr. z. Klin. der Tuberkulose*, xi, Heft 1.

62. Tiegel, 'Ueber operative Lungenstauung und deren Einfluss auf die Tuberkulose.' 40te Versamml. der deutsch. Gesellsch. f. Chir., Ref. in *Münch. mediz. Wochenschr.*, 1911, 1044.

63. Toussaint, 'Sur la marche de la tuberculisation pulmonaire. Influence du pneumothorax,' *Thèse de Paris*, 1880.

64. Warnecke, 'Beitrag zur pathologischen Anatomie des künstlichen Pneumothorax,' *Brauer's Beitr. z. Klin. der Tub.*, xvi, Heft 2, 171–82.

65. August Weiss, 'Ueber Komplikationen bei der Behandlung mit künstlichem Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xxiv, Heft 3, 333–65.

66. Wellmann, 'Klinische Erfahrungen in der Behandlung mittels künstlichem Pneumothorax,' *Beitr. z. Klin. der Tuberkulose*, xviii, Heft 1, 81–116.

67. Würtzen and Kjer-Petersen, 'Om kunstig Pneumothorax,' *Hospitalstidende*, 1908.

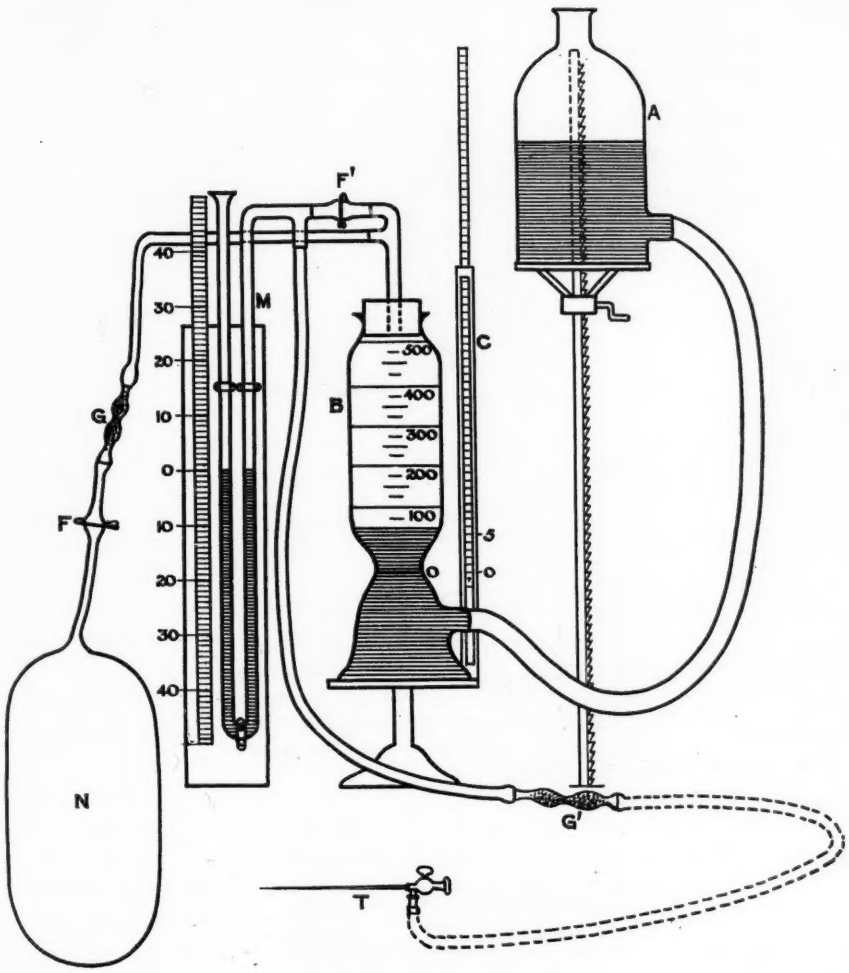


Fig. 1

A. Movable bottle. B. Fixed graduated cylinder containing Nitrogen. C. Sliding rule to measure the distance between the level of liquid in A and B. M. Water manometer. N. Nitrogen bag. T. Trocar. G G'. Glass tubes containing sterilized cotton-wool for the filtration of nitrogen. F F'. Forceps interrupting communication between nitrogen bag and graduated cylinder (F), between cylinder and manometer with trocar (F').

In this drawing, the level of liquid in A is much higher than in B. The nitrogen in B is under positive pressure. The communication being interrupted between B and the manometer by forceps F', the manometer is under atmospheric pressure.

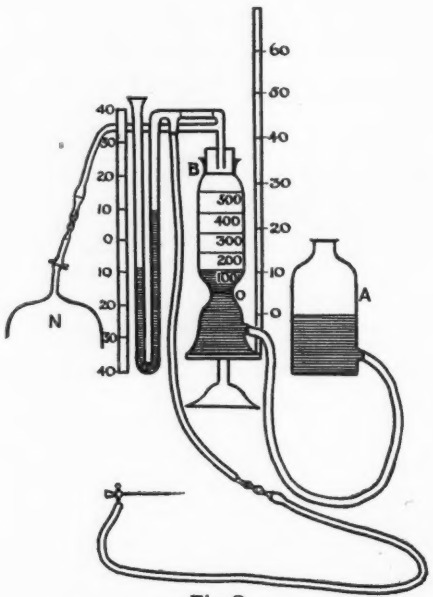


Fig 2

The level in A is 10 centimeters lower than in B. The pressure in B is accordingly a negative pressure measured by 10 centimeters of water. The manometer communicates with the cylinder B and shows a negative pressure of 10 centimeters.

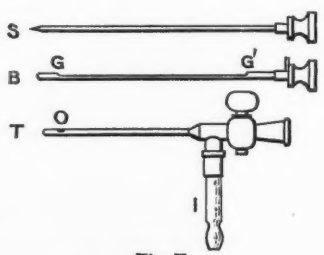


Fig 3

S. Sharp stilette.
B. Blunt stilette, with groove G-G'.
T. Trocar with side opening O.
I. Glass index where the blood appears if the trocar has entered a blood vessel.

THE USE OF THE OXYDASE REACTION IN THE DIFFERENTIATION OF ACUTE LEUKAEMIAS

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With Plates 16 and 17

Until a few years ago all cases of acute leukaemia were classified as lymphatic. It was recognized that in such cases the lymphatic glands and the spleen might show little evidence of a leukaemic change, while the bone-marrow might be extensively altered, but the fact that the leucocytes in the blood and in the organs were non-granular was proof, according to Ehrlich's (5) view (1905), of their lymphocytic nature, and the disease was regarded as essentially lymphatic.

An advance from this standpoint was first made possible after embryological research had shown that the bone-marrow of the foetus is, in its earlier stages, composed of non-granular cells, from which the granular myelocytes take origin later. This fact was found to explain the nature of certain puzzling cases of leukaemia with a 'mixed' blood-picture, myelocytes and lymphocytes being both present together in excess: these 'lymphocytes' were really the non-granular precursors of the myelocytes and their presence merely indicated a more than usually embryonic type of blood-formation, and not the co-existence of two different forms of leukaemia (1).

An important contribution to this subject was then made by W. H. Schultze (18). He described a case of acute leukaemia in which the leucocytes in the blood numbered 560,000 per cubic millimetre, and were almost exclusively large mononuclear cells with basophil, non-granular protoplasm: clinically an acute lymphatic leukaemia. By thorough histological examination of the organs after death Schulze was able to show that the lymphatic germ-centres in the spleen, lymph-glands, and lymphatic tissues generally had in this case remained quite inactive, and that a remarkable development of large non-granular cells had taken place in the bone-marrow, in the pulp of the spleen, and in the medullary parts of the lymph-glands. He concluded that these large cells were in reality non-granular marrow-cells and that the case was one of acute myeloid leukaemia, although only a very small proportion of granular leucocytes was present in the blood and blood-forming organs. Other cases of acute myeloid

leukaemia were subsequently described by various observers, though only those confirmed by anatomical proof were accepted as absolutely free from doubt. In some of these cases, even cases of very acute course, the blood-picture showed fairly large proportions of granular myelocytes and transitional stages in the development of these from myeloblasts, e. g. cases of Meyer and Heineke (12), Fabian, Naegeli and Schatiloff (6). Only a few exhibited the extremely lymphoid character of that described by Schultze, e. g. case of Pappenheim and Hirschfeld, 1908 (15). With regard to the possibility of differentiating such cases as the latter clinically by examination of the blood there was always some dissension. The proportion of myelocytes present, being small, might have been of the nature of the 'irritation-myelocytosis' which may occur in lymphatic leukaemias. Reliance was placed by some observers on the finer histological characters of the embryonic leucocytes to distinguish myeloblasts, the non-granular marrow-cells, from lymphoblasts, the corresponding mother-cell of the lymphocytes.

Naegeli (13), who first named and described the myeloblasts, stated that the nuclei of these cells possess three or four nucleoli; those of lymphocytes never more than two. This is certainly true in normal embryological blood-formation, but it has been suggested that under pathological conditions this criterion may not be reliable (2).

In general, myeloblasts are larger cells and have a greater body of protoplasm than lymphocytes, but large forms of lymphocyte occur and small forms of myeloblast with narrow protoplasm are known (Naegeli (13) 1900), and may even form a large proportion of the cells in the blood in leukaemia (8).

'Azure granules' of a certain type are peculiar to lymphocytes, but they do not occur in all lymphocytes. Schridde's fuchsinophil granulation was at first supposed to be characteristic of lymphocytes, but it has later been shown that myeloblasts also contain granules stainable by the Altmann-Schridde method (3).

The chromatin of myeloblast nuclei, as in myelocytes, is arranged in a fine regular network, while in lymphocyte nuclei it is in the form of coarser and more irregular bands (13). Whether this invariably holds good under extreme pathological conditions is not yet determined.

In view of the divergence of opinion on this subject it was suggested by Schultze (19) that the chemical behaviour of the cells might afford a surer means of differentiation, and, in fact, he found that in the case already referred to and in another similar case, the majority of the cells forming the leukaemic infiltrations in the organs, though chiefly non-granular, gave the indophenol-oxydase reaction, thus proving their myeloid nature. Confirmatory evidence of the value of this reaction has been obtained in a number of cases. Peters (17) obtained a positive oxydase reaction in 'almost all' the large cells, in a case where the leucocytes numbered 57,000 per cubic mm. and 96 per cent. were myeloblasts. Marchand (10) obtained a similar result in a case with 250,000 leucocytes per cubic mm., almost all large non-granular cells. In the case described by Isaac and Cobliner (8), where the blood contained 33,000 leuco-

cytes per cubic mm., with 8 per cent. of myeloblasts and 81 per cent. of cells resembling small lymphocytes, all of these cells were said to give the oxydase reaction in blood-films. The blood-formation in the organs was of the myeloid type as described by Schultze, and showed a greater proportion of large myeloblasts than would have been expected from the blood-picture. In sections of the organs only the large cells gave a positive oxydase reaction.

A case described by Kahn (9) is noteworthy. In this case the blood showed 200,000 leucocytes per cubic mm., and almost all were large non-granular cells. Of these 'about half' gave a positive oxydase reaction of varying degrees of intensity. The myeloid nature of the case was confirmed by post-mortem examination. In discussing the case Kahn states that the absence of the oxydase from a large proportion of the myeloblasts is due to the 'toxic effect of the leukaemic poison'. He gives it as his opinion also that 'if in an acute leukaemia even only a proportion of the leucocytes, which by ordinary staining methods are non-granular, give the oxydase reaction, this proves the occurrence of transitions between non-granular and granular cells, and the diagnosis of myeloid leukaemia may be made with certainty'.

Thomas (21) has also observed absence of oxydase reaction in the large non-granular cells in the organs in a case of sub-acute myeloid leukaemia, in which the blood-picture was of the 'mixed' type.

It is noteworthy that since Schultze in 1906 first accurately differentiated acute myeloid leukaemia of the extreme lymphoid type, most, at any rate, of the acute large-celled leukaemias reported have also been found to be myeloid. It has even been suggested that all acute leukaemias are of myeloid nature (8), (9), (20). However, in a case of acute large-celled leukaemia described by Graetz (7) the large cells appeared to be derived from enlarged lymph-follicles and they gave no oxydase reaction. Graetz considered this case to be lymphatic. In another case of acute leukaemia described by Marchand (11) the cells in the blood were chiefly small lymphocytes, and they were found to take origin from lymph-follicles. Here also the oxydase reaction was negative.

The total number of acute leukaemias reported in which the oxydase test has been applied is not yet very large, and as these cases are not of very common occurrence opportunity has been taken to apply the test in some recently observed, and to control the results as far as possible by histological examination of the blood-forming organs.

Case I. R. McC., male, aged 59 years, was admitted to the Glasgow Western Infirmary on October 27, 1911, under the care of Prof. Samson Gemmell, suffering from pains in the back, weakness, and loss of weight of about three months' duration.

When examined on admission he was somewhat wasted and his skin showed a yellow pallor. There was evidence of enlargement of both the liver and the spleen. A haemorrhage was visible in the left retina.

The blood estimation gave:

Red-blood corpuscles	2,030,000 per cubic mm.
Haemoglobin	53 per cent.
Leucocytes	?

The red-blood corpuscles were well coloured, and there was little polychromatophilia. Poikilocytosis was present. Megaloblasts and myelocytes were present. No differential count was made of the leucocytes.

On November 3 the blood-count gave:

Red-blood corpuscles	2,930,000 per cubic mm.
Haemoglobin	50 per cent.
Leucocytes	13,000 per cubic mm.

On November 4, 0·4 gramme salvarsan was injected intravenously.

November 8. The patient's condition was worse.

Red-blood corpuscles	1,460,000 per cubic mm.
Haemoglobin	40 per cent.
Leucocytes	56,000 per cubic mm.

November 10. Symptoms progressively worse.

Temperature 103·2°. Pulse 104. Resp. 32.

November 13.

Red-blood corpuscles	1,283,000 per cubic mm.
Haemoglobin	32 per cent.
Leucocytes	203,000 per cubic mm.

He died on November 16, 1911.

The Examination of the Blood. Films of blood obtained on three different dates, November 8, 15, and 16, were subjected to careful examination. Differential counts of 1,000 cells each were made on films stained by Jenner's eosin-methylene-blue and by Ehrlich's triacid stain, and use was also made of Pappenheim's methyl-green-pyronin. This latter, a mixture of two basic dyes, gives the nuclei a bluish-green colour and stains basophil protoplasm red in a degree corresponding to the degree of basophilia. It is very useful in the recognition of myeloblasts of varying degrees of ripeness, but as it does not stain eosinophil or neutrophil granules it is hardly suitable for differential counts. The results of the differential counts on the dates mentioned were as follows:

November 8. Leucocytes, 56,000 per cubic mm.

	Jenner.	Triacid.
Neutrophil polymorphonuclears	5·4 %	6 %
Neutrophil myelocytes	3·2 %	7·6 %
Eosinophils	0·2 %	0·2 %
Basophils	—	—
Myeloblasts	89·6 %	82·8 %
Small lymphocytes	1·6 %	3·4 %
	100·0 %	100·0 %

Nine megaloblasts and twelve normoblasts were seen while counting 2,000 leucocytes.

November 15. Leucocytes 203,000 per cubic mm.

	Jenner.	Triacid.
Neutrophil polymorphonuclears	3·1 %	4·9 %
Neutrophil myelocytes	5·2 %	11·9 %
Eosinophils	—	0·4 %
Basophils	1·4 %	0·2 %
Myeloblasts	89·4 %	80·9 %
Small lymphocytes	0·9 %	1·7 %
	100·0 %	100·0 %

Five megaloblasts and four normoblasts seen while counting 2,000 leucocytes.

November 16.

	Jenner.	Triacid.
Neutrophil polymorphonuclears	1·8 %	2·5 %
Neutrophil myelocytes	3·8 %	8·3 %
Eosinophils	—	—
Basophils	—	—
Myeloblasts	93·0 %	87·3 %
Small lymphocytes	1·4 %	1·8 %
	100·0 %	100·0 %

One megaloblast and four normoblasts seen while counting 1,000 leucocytes.

It may be noted here that among the megaloblasts are included a few very embryonic forms, the protoplasm of which is markedly basophil and entirely lacking in haemoglobin. These cells are easily recognized by the character of the nucleus, which is similar to that of the ordinary megaloblast. (Cf. Scott (20), Pappenheim and Hirschfeld (15), and others.)

The polymorphonuclear leucocytes seen in the films are, for the most part, of normal aspect, but in some the granules are more faintly stained than normal, and in others they are diminished in number.

Under the heading of neutrophil myelocytes are included all mononuclear and transitional cells which contain neutrophil granules, and while many of these have the usual characters of neutrophil myelocytes with well-developed granules a considerable proportion of younger cells were seen in which part of the protoplasm is still basophil and the neutrophil granules are few in number. It will be noted in a review of the various counts that the percentage of myelocytes is always greater in the count of a film stained with triacid than in the corresponding film stained with Jenner, and this increase of myelocytes is balanced by a diminution in the number of myeloblasts. This may be considered to be almost a rule in comparative estimations of the kind, and depends on the presence of cells with granules which give the neutrophil tint with the specific neutrophil stain but which have too slight an acidophil tendency to pick up the eosin out of the eosin-methylene-blue mixture.

The eosinophil and basophil leucocytes are present only in very small numbers, as is usually the case in acute myeloid leukaemia. The cells counted as small lymphocytes are mononuclear cells with basophil protoplasm, and are seldom much, if at all, larger than red corpuscles.

All the remaining cells, amounting to from 80 to 93 per cent. of the total leucocytes in the various estimations, have been classed together as myeloblasts, the non-granular precursors of the myelocytes. As it is important to indicate to what extent these cells possess oxydase properties it will be necessary to describe them in some detail. Their diameter varies from 10 to 25 microns. Their nuclei, which, in films stained by Jenner, are always paler than the protoplasm, are round, oval, indented, or even sometimes lobed. With triacid staining the nuclei are pale-green in colour and closely surrounded by the protoplasm, which is of varying shades of pale brown and shows no neutrophil granulation. In films stained by Jenner the protoplasm appears reticular and more basophil

than the nucleus, but there is a certain lack of uniformity in individuals which renders necessary the recognition of three types. *First.* A small proportion, 3 per cent. of the total leucocytes, were characterized by the density and uniformity of the basophil protoplasmic reticulum, which stains deep crimson with Pappenheim's stain and deep blue with Jenner's stain. In the nuclei of these cells three or four nucleoli are generally somewhat indistinctly visible. *Second.* The largest group, amounting to 68 per cent. of the total leucocytes, had basophil reticular protoplasm, but this shows, generally over a small area only, an appearance of widening of the reticular meshwork sometimes accompanied by a very slight acidophil staining of the clearer matrix in the meshes, though no granules are visible by any staining method. The area of protoplasm so affected often lies against an indentation of the nucleus.

The *third* group consists of cells similar to the second, but with protoplasm which contains more or less numerous basophil granules. These granules are scattered throughout the protoplasm and they vary in size, the smallest being the size of neutrophil granules, the largest three to four times that size. With Jenner's stain they have a violet tint; with Pappenheim's stain they appear red or sometimes brown. These cells amount to about 22 per cent. of the total leucocytes.

The separation of these three types is not, of course, intended to indicate any difference in nature of the cells, but merely for convenience of description. They merge closely into one another and no doubt represent different stages of maturity of the one class of cell, as is indeed indicated by the oxydase reaction.

Several counts were made on films prepared to demonstrate this reaction, the procedure being as follows: The films were fixed by immersion in 1 per cent. osmic acid for five seconds. They were then washed thoroughly in running water for five minutes and brought into a mixture of equal parts of:

Dimethylparaphenylenediamine . .	$\frac{1}{5}$ per cent. aqueous solution
and Alpha-Naphthol	saturated aqueous solution

for periods varying up to half an hour. The films were then washed for a few minutes in running water and mounted on slides in a mixture of equal parts of commercial water-glass and tap-water. Normal blood-films treated in this way show a deep blue staining of the polymorph leucocytes due to formation of indophenol in their protoplasm; this occurs in virtue of the oxydizing ferment or oxydase present in these cells. For details of the reaction see Schultze (1909) (19) and Dunn, 1910 (4).

In films from the present case stained by this method for a short time, five minutes, it is found that the majority of the leucocytes show blue staining, some very densely, others very faintly, while all intermediate degrees of staining occur. A certain proportion remain entirely unstained. In films treated for longer periods the depth of blue staining increases and the number of unstained cells is reduced to a minimum, but never quite abolished (Fig. 1). As a result of several estimations it is found that about 10 per cent. of the leucocytes show

no reaction. It is difficult to give an absolutely accurate figure as the leucocytes often lie in groups, and those which give a strong reaction produce a certain amount of precipitation of indophenol on other cells lying beside them. By counter-staining with Pappenheim's stain it is seen that the cells which give no reaction are either small lymphocytes or myeloblasts with strongly basophil protoplasm. These are believed to include the first type of myeloblast. Of the cells which give a reaction a large number show only a faint diffuse blue staining of one area of protoplasm, often opposite to an indentation of the nucleus. These cells represent roughly the second and third types of myeloblast. The granular myelocytes and polymorphs are stained intensely blue, just as they are in films from chronic myeloid leukaemia.

The following is an account of the post-mortem examination, which was performed twenty-four hours after death, by Professor Muir:

External Appearances. The body was that of a powerfully built man, slightly emaciated. The skin had a lemon tint. *Thorax.* The pericardial sac was normal. The heart was somewhat enlarged, especially the left side. The fat on the surface was moderate in amount. The arterial valves were competent. The mitral orifice measured 1·5 inches in diameter; the tricuspid 1·8 inches. The valve-segments were healthy. The left ventricle was slightly hypertrophied and dilated; the right ventricle was also slightly hypertrophied. The myocardium showed extreme patchy fatty degeneration.

Both pleurae were obliterated by fibrous adhesions. There were some fibrous nodules, the remains of old tuberculous lesions, in the upper lobe of the right lung. The lungs were oedematous. There was a patch of early pneumonic consolidation in the upper part of the lower lobe of the left lung.

Abdomen. An inguinal hernia was present on each side and there was some chronic peritonitis around the inguinal rings. There was no ascites. The *liver* was much enlarged and weighed 5 lb. 14 oz. There were a few fibrous adhesions over its upper surface. The organ was of fairly firm consistence and on section was of a somewhat pale brownish-red colour. The portal tracts were somewhat more distinct than normal. A very intense reaction for free iron was given on testing with hydrochloric acid and potassium ferrocyanide. The *spleen* was enlarged and weighed 1 lb. 3 oz. It was fairly firm in consistence and of rather pale reddish colour. The Malpighian bodies were visible, but not prominent. A well-marked reaction for free iron was given. The right *kidney* was somewhat enlarged and weighed 6 oz. The capsule stripped fairly readily. The surface generally was of pale yellowish colour and there were numerous slightly prominent areas measuring $\frac{1}{8}$ to $\frac{3}{8}$ inch in diameter, of whitish colour. On section these areas presented ill-defined margins. They suggested foci of leucocytic infiltration. The colour of the kidney otherwise suggested the presence of fatty degeneration. The left kidney was similar in appearance, the whitish areas being less numerous. The stomach and intestines presented no change of note. The bone-marrow in the right femur was of greyish-pink colour in the upper two-thirds of the bone, the lower third being fatty. This grey marrow was moderately firm in consistence and had a somewhat translucent appearance. The rib-marrow was of pale-red colour. The deep cervical lymphatic glands were all somewhat enlarged, the largest measuring $1\frac{1}{4}$ inches long by $\frac{3}{4}$ inch in diameter. On section they were all of a pale dull greenish colour, which faded rapidly on exposure to the air. The axillary glands were of the size of small beans, of firm consistence, and of greenish colour. The mesenteric, retroperitoneal, and inguinal glands were not apparently enlarged,

but were of firm consistence. On reaction they were of pale greyish-pink colour. The tonsils were slightly enlarged and on section were of greenish colour.

Histological Examination. Portions of the various organs were fixed in 5 per cent. formalin and in corrosive sublimate solution, and some portions were fixed in Formol-Müller (1 in 10) for examination by the Altmann-Schridde method. The stains employed were haemalum and eosin, triacid, methyl-green-pyronin, Leishman's method for sections, and the Altmann-Schridde method. The oxydase test was applied to sections of tissues fixed in formalin and cut both by freezing and by the paraffin method.

The femur-marrow in sections appeared as a solid cellular tissue from which the fat had almost entirely disappeared. The cells composing it were of fairly uniform large size with abundant protoplasm. The great majority of them had basophil protoplasm and showed no granules, and they corresponded with the myeloblasts seen in the blood. Some of them showed mitotic figures. Eosinophil cells and neutrophils were scattered irregularly throughout, but nowhere numerous. Nucleated red corpuscles were also seen throughout the sections. Megakaryocytes were few in number. The appearances in films of femur and rib-marrow confirmed the great predominance of myeloblasts and the scantiness of neutrophils and eosinophils. In the films stained by Jenner or Leishman numerous myeloblasts with metachromatically stained violet granules were seen as in the blood. The sections of marrow treated with the oxydase reagent showed blue staining of almost all the cells. A few scattered cells stained more intensely than others and some small groups showed very little staining (Fig. 2).

In the spleen the lymph-follicles appeared small and were composed of small lymphocytes which contrasted sharply with the large round cells filling the pulp. The pulp was increased in amount so that the lymph-follicles appeared widely separated. These large cells in the pulp corresponded with those in the bone-marrow. A rather larger proportion of granular cells was present here, and nucleated red cells were also seen. A considerable amount of iron-pigment was present in the phagocytes. In sections stained by means of the oxydase reaction the pulp appeared almost uniformly blue and the unstained lymph-nodes stood out in sharp contrast (Fig. 3).

In the liver the portal tracts showed fairly extensive infiltration by cells similar to those in the marrow. Some groups of these cells could also be observed in dilated capillaries in the liver lobules. The liver-cells contained iron. The leukaemic infiltrations presented a striking picture in sections stained by the oxydase method (Fig. 4).

The pale nodules in the kidneys proved to be areas of massive myeloid infiltration. The great majority of the cells were myeloblasts, but granular myelocytes and nucleated red corpuscles were also seen. In sections stained by the oxydase method these nodules and the cells infiltrating the kidney generally stood out in sharp contrast to the unstained tubules (Fig. 5).

The cervical and other lymphatic glands exhibited extreme myeloid infiltration of the medulla. In the larger cervical glands only a few small lymph-nodes remained, easily recognizable, by the small lymphocytes forming them, among the masses of larger marrow-cells. The peripheral and medullary sinuses were filled with marrow-cells. In the smaller glands the amount of residual lymphatic tissue was greater. Its amount could be estimated with great accuracy in sections stained for oxydase, where it appeared in the form of pale areas surrounded by the blue-stained myeloid tissue (Fig. 6).

In sections of the bone-marrow and other organs stained by the Altmann-Schridde method no granules resembling those found in lymphocytes were observed in any of the large mononuclear cells.

There is no suggestion of development of genuine tumour-growth in relation to any of the infiltrations in the organs.

Summary. The onset and course of this case are not those of the most acute forms of leukaemia, and though serious symptoms existed only for four months it is possible that leukaemic changes in the organs had been present with sub-leukaemic blood-picture for some time previously. However, the rise in the number of leucocytes in the circulation occurred with great rapidity, from normal limits to over 200,000 per cubic mm. in ten days' time, and the leucocytes present show very embryonic characters, as nearly 90 per cent. are, in Ehrlich's sense, non-granular. Examination of the blood by ordinary staining methods certainly suggests that these non-granular cells are myeloblasts, and that the myelocytes are developing from them. A certain proportion of typical myeloblasts such as Naegeli described, and such as may be observed in the marrow or the liver of a five-months' foetus, were present, and an unbroken chain of transitional forms may be observed between these and the granular myelocytes. The oxydase reaction is positive in the great majority of these cells and is positive in greatly varying degree in different examples, a fact which confirms the idea that transitional forms of many varying degrees of maturity are represented.

The histological examination of the organs shows that the type of blood-formation is myeloid, as described by Schultze, and the myeloid nature of the deposits is again fully confirmed by the positive oxydase reaction.

Case II. T. H., male, aged 13 years, was admitted to the Glasgow Western Infirmary on December 1, 1911, under the care of Dr. Barclay Ness. He was suffering from progressive general weakness of three months' duration, and had had severe headaches, ulceration of and bleeding from the gums, and also haematemesis. Ten days before admission purple spots suddenly appeared on the skin. The patient had tuberculosis of the left knee, with sinus-formation, of four years' standing.

On admission he was much wasted and his skin was very pale. A fairly profuse purpuric eruption was present. The gums were ulcerated and bled readily. The temperature was 99°, pulse 116 per minute, respirations 24 per minute.

On physical examination the liver was found to be enlarged and palpable. The spleen also was enlarged and could be felt under the costal margin. There was no palpable enlargement of lymphatic glands. The urine contained albumin but no blood. Blood was present in the faeces.

The patient went rapidly downhill. The temperature rose to 101°, the pulse-rate to 136, and the respiration-rate to 32 per minute. He died on December 3, two days after admission.

The blood was examined on December 2.

The red corpuscles numbered 2,200,000 per cubic mm. The haemoglobin amounted to 40 per cent. Colour index 0·9. The leucocytes numbered 81,000 per cubic mm.

Films were stained by Jenner's stain, triacid, methyl-green-pyronin, haemalum and eosin, and by the oxydase method. On examination of a Jenner-stained film the red corpuscles showed only slight poikilocytosis and variation in size. There was little polychromatophilia or granular degeneration. The red corpuscles stained fairly well with eosin. Four megaloblasts and two normoblasts were seen during a count of 1,000 leucocytes, and a few early megaloblasts without haemoglobin were observed throughout the films. The most striking feature was the presence of numbers of large non-granular cells with

basophil protoplasm, which seemed at first to be the only form of leucocyte present.

A differential count of 1,000 leucocytes on a film stained with Jenner gave the following figures:

	per cent.
Neutrophil polymorphonuclears	0·6
Neutrophil myelocytes	5·5
Eosinophil polymorphonuclears	0·3
Eosinophil myelocytes	0·2
Basophil (myelocyte)	0·1
Large non-granular mononuclears	88·3
Smaller non-granular mononuclears	5·0
	100·0

A similar count on a film stained with triacid gave:

	per cent.
Neutrophil polymorphonuclears	2·0
Neutrophil myelocytes	3·5
Eosinophil polymorphonuclears	0·1
Eosinophil myelocytes	0·4
Basophil polymorphonuclears	0·2
Large non-granular mononuclears	88·5
Small non-granular mononuclears	5·3
	100·0

The neutrophil polymorphonuclears seen were of fairly normal appearance; in some the granules stained rather faintly. In some of the neutrophil myelocytes the protoplasm was faintly basophil, indicating immaturity. The large non-granular mononuclear cells, which constituted such a large proportion of the total, showed considerable variation in size, ranging from 12 to 30 microns in diameter. The nucleus in these cells was, with Jenner's stain, paler than the protoplasm, and regularly showed from four to six definite nucleoli (Fig. 7). The nucleus occupied from four-fifths to seven-eighths of the cell body, and was generally round or oval, but occasionally indented or even lobed. Mitotic figures were observed in a few in the course of many examinations. The protoplasm exhibited an intensely basophil reticulum without visible granulation, and surrounded the nucleus closely. It was somewhat labile and easily crushed. Vacuoles were present in some cells, but Auer's bodies were never observed in specimens stained with Giemsa or Leishman's stain. In a very few examples metachromatic violet (pre-neutrophil) granules were seen. While in the great majority the protoplasmic reticulum was close and homogeneous, a certain percentage, amounting to 10 per cent. of the total leucocytes, exhibited a slight degree of loosening and transparency of it, so that the protoplasm appeared pale though still darker than the nucleus. This was regarded as an evidence of ripening of these cells.

Of the cells counted as small mononuclears the majority were simply small examples of the large ones already described, but it was noticeable that the nucleoli were less easily seen in these cells. It is possible that some of them were ordinary small lymphocytes, but this could not be accurately estimated.

With triacid staining the protoplasm of the non-granular cells appeared

brown and the nuclei bluish-green. With pyronin-methyl-green the nuclei appeared green, nucleoli crimson, and protoplasmic reticulum crimson. With this stain also the cells with the looser reticulum appeared distinctly paler than the others.

From the histological features of the large cells in this case it was considered certain that they were myeloblasts, and that though only 6 per cent. of granular cells were present, the case was one of myeloid leukaemia. The oxydase test was then applied and careful estimations made extending over 4,000 leucocytes in different films. The result of this investigation gave :

		per cent.
Positive reaction	well marked	12
	faint	2
Negative reaction		86

(See Fig. 8.)

The reaction really showed great variations in the degree of intensity in the various cells, being most pronounced in the polymorphonuclears and in the myelocytes. In the 2 per cent. which gave a faint reaction this showed as a slight diffuse blueness usually of one area of protoplasm and generally of the broadest part of the protoplasm, lying opposite an indentation of the nucleus. None of those cells counted as small mononuclears showed the faintest trace of a reaction.

As the total proportion of cells which gave a positive reaction (14) exceeded the total proportion of granular cells (6 per cent.) by 8 per cent., it was obvious that this 8 per cent. must be made up by some of the large non-granular cells, and it no doubt represents those non-granular cells in which the protoplasmic reticulum appeared looser. As those paler cells are distinguished from the great majority of the non-granular cells only by this protoplasmic character, it seems certain that they represent transitional stages in the ripening of the latter towards the granular forms. In other words, the majority of the non-granular cells, though they give a negative oxydase reaction, are embryonic myeloid cells, or myeloblasts.

Post-mortem examination (performed forty hours after death).

The body was that of an emaciated boy. The skin generally was pale, and there was a fairly extensive petechial rash. There was some swelling and haemorrhage visible along the gums. An open sinus was present above the left knee, communicating with the interior of the joint.

The pericardial cavity contained an ounce of blood-stained fluid. Both layers of pericardium exhibited numerous minute haemorrhages. The valves of the heart were normal; the cavities were slightly dilated; the muscle exhibited diffuse fatty change. The pleurae were free from adhesions: each pleural sac contained 4 oz. of blood-stained fluid, and petechiae were present in both layers of pleura. The lungs were well aerated and free from oedema: they exhibited no gross lesion.

The peritoneal cavity contained 2 oz. of blood-stained fluid, and minute haemorrhages were present here and there throughout the membrane.

The liver weighed $1\frac{3}{4}$ lb. and did not appear enlarged. On section the

liver substance showed evidence of diffuse fatty degeneration. The portal tracts did not appear enlarged. On treatment with hydrochloric acid and potassium ferrocyanide a very faint green colour was given, indicating presence of free iron.

The spleen, which weighed 12 oz., was much enlarged, and its edges were rounded and the capsule tense. The organ crackled when handled, on account of the presence of bubbles of gas from a gas-forming organism. On section the pulp was of dark-red colour and somewhat diffluent. The lymph-nodes were quite obscured. The iron reaction was almost nil. The *kidneys* were pale and yellowish in colour from fatty degeneration. The iron reaction was negative. The mucous membrane of the *stomach* showed numerous petechial haemorrhages. The *intestinal* mucous membrane and the Peyer's patches showed no departure from normal.

The mesenteric and retroperitoneal lymph-glands were not enlarged, but were slightly firmer than normal.

The tonsils were slightly swollen and superficially ulcerated. The cervical lymphatic glands were very slightly enlarged and were firm, oedematous, and of dark-red colour. The axillary and inguinal lymph-glands were not enlarged, but were slightly firmer than normal.

The rib-marrow was pale reddish in colour and very fluid and translucent. It contained little fat. The marrow of the left femur was of pale greyish-pink colour throughout, with areas of congestion and some small haemorrhages.

The left knee-joint showed a fairly extensive tuberculosis affecting chiefly the synovial membrane and involving the bones only superficially.

Histological Examination.

Sections of the femur-marrow showed total disappearance of fat-cells. The whole tissue was made up of almost uniform large cells, with basophil protoplasm, packed closely together and supported by a very light reticulum, hardly visible. Mitotic figures were present in considerable numbers. In sections stained by Leishman's method a very few eosinophil and neutrophil myelocytes could be observed. Red corpuscles, a few nucleated, were also scattered quite irregularly. Very few megakaryocytes could be seen. The appearances in dry films confirmed the above. In wet-fixed films (corrosive sublimate) the fine reticulum of chromatin in the nuclei of the large cells was well shown. Films and sections treated by the oxydase method showed a very few scattered cells with positive result, and these were for the most part eosinophil or neutrophil myelocytes. The proportion of matured cells was indeed much smaller in the bone-marrow than in any of the organs showing leukaemic infiltrations.

Spleen. The structure of this organ was to some extent altered by the presence of small gas cavities, but many areas were sufficiently well preserved to show the pathological changes, and the staining properties of the cells were little impaired. The lymph-follicles were few in number and widely separated; of many only the atrophied remains were visible and they were composed of small lymphocytes only. The pulp contained a large number of red-blood corpuscles, and also a large proportion of the large basophil mononuclear cells. These were scattered diffusely and in groups, and were accompanied by small numbers of eosinophil and neutrophil myelocytes. In one or two places they occurred in dense round nodes of more active growth resembling follicles, and these sometimes occurred near the remains of atrophied lymph-follicles, but could be readily distinguished from them: they possessed no central vessel. They could be seen to exert pressure on the surrounding tissues by activity of growth. The oxydase reaction was positive in a considerable proportion of the cells throughout the pulp: mostly granular cells, but also faintly in some of the non-granular.

In the liver the portal tracts contained rather small but dense accumulations

of the large mononuclears, with a few granular myelocytes and nucleated red cells. The margins of these infiltrations were irregular, and some accumulations of similar cells could be observed in dilated capillaries in the lobules. Mitoses were frequently observed (Fig. 9). The oxydase reaction in sections of liver showed a small but uniformly distributed proportion of positively reacting cells throughout the infiltrations. The proportion of these certainly exceeded the small proportion of granular cells present (Fig. 10).

In the kidney there was a scanty distribution of leukaemic cells in places in the connective tissue.

In the cervical and axillary lymphatic glands the lymphatic nodes were composed of small lymphocytes only and were of small size. The large basophil mononuclears appeared in considerable numbers in the medullary sinuses and also in the peripheral sinus, and were also observed in the gland-tissue in the immediate neighbourhood of these sinuses, where they were undergoing proliferation and forming in some places small round collections of cells, similar to those in the spleen and quite apart from the lymph-nodes. Numerous red corpuscles were also present in the sinuses and were seen being taken up by phagocytes there. The changes in some mediastinal glands were similar to those described. Some glands from the left groin showed merely fibrous thickening of the medulla, the result of chronic inflammatory change, and no leukaemic infiltration was recognizable.

In several mesenteric glands the lymphoid tissue was almost entirely destroyed, but persisted in the form of irregular areas composed of small lymphocytes only. In the medullae of these glands there were numerous neutrophil and eosinophil myelocytes, and also nucleated red corpuscles. These cells were in greater abundance here than in any other tissue examined. They were accompanied by large numbers of the large non-granular mononuclears. The oxydase reaction was present in a very considerable proportion of cells in the infiltrations here.

The tonsils, which showed slight superficial ulceration, exhibited a change, which was at variance with the findings recorded elsewhere. The lymph-nodes here were enlarged, and were composed of large cells hardly distinguishable by any feature from those forming the infiltrations elsewhere in the body. Similar cells were also present in considerable numbers around the crypts and penetrating into the epithelial layers.

There was nothing suggestive of genuine tumour-growth in any of the organs.

Summary.

This case presents a typical picture of acute leukaemia. Its brief course is marked by haemorrhages into the skin and from the mucous membranes, by fever, and by ulcerative gingyvitis. The lymphatic glands are not enlarged. The blood-picture shows a considerable increase of leucocytes, of which the great majority are large non-granular cells. These present the typical characters of Naegeli's myeloblasts, and transitional forms between them and myelocytes are present, though scanty. The oxydase reaction conclusively proves the myeloid nature of a certain proportion of these, which differ from the others only by a slight alteration of the protoplasm indicative of ripening. The absence of the reaction from the majority of them is to be explained by their very embryonic character rather than by pathological suppression of a function already developed. They correspond accurately with the first type of myeloblast described in Case I, which also gave negative oxydase reaction. The type of the blood-

formation in the marrow, in the pulp of the spleen, and in the medullae of lymph-glands, and the atrophy or inactivity of the lymph-nodes are confirmatory of the view, based on the blood-examination, that the case is one of acute myeloid leukaemia.

This case differs from Case I, not only in being more acute and of more embryonic type, but also in showing much less advanced changes in the organs. In the cervical glands, for example, there is little enlargement, and the condition of leukaemic infiltration is at an early stage, which renders possible some observations on its mode of occurrence. It is seen that the lymphatic tissue remains indifferent and is composed of small lymphocytes: the *myeloblasts are most numerous in the sinuses and in the neighbourhood of these: one or two foci of more massive development of myeloblasts which are present are also in the neighbourhood of the sinuses.* (Similar foci were observed in spleen and in mesenteric glands.) These appearances, so far as they go, are in favour rather of the metastatic origin of the myeloid tissue than of the metaplastic development of it from cells previously present in the organs.

Case III. In this case, unfortunately, no post-mortem examination was made after death, so that the organs could not be examined histologically.

The patient was a girl of 11 years of age, and presented symptoms of acute leukaemia. Accurate details are not available.

The blood-examination showed:

Red-blood corpuscles	1,160,000 per cubic mm.
Haemoglobin	45 per cent.
Leucocytes	250,000 per cubic mm.

Differential estimations of the leucocytes gave the following results:

Jenner's Stain.	*1,000 Leucocytes.* per cent.
Neutrophil polymorphonuclears	2·2
Neutrophil myelocytes	0·3
Large non-granular mononuclears	93·5
Small lymphocytes	4·0
	100·0

Triacid.	
Neutrophil polymorphonuclears	1·7
Neutrophil myelocytes	0·6
Eosinophil polymorphonuclears	0·6
Large non-granular mononuclears	92·8
Small lymphocytes	4·3
	100·0

Oxydase Reaction.	
Positive reaction	3·3
Negative reaction	96·7
	100·0

Thirty normoblasts and four megaloblasts were seen during a count of 2,000 leucocytes. Some early megaloblasts without haemoglobin were observed throughout the films.

In this case it will be seen that the Jenner and triacid counts give almost identical figures: 97 per cent. of non-granular and 3 per cent. of granular cells, and that the oxydase reaction is negative in all but the granular cells. Accordingly, this reaction gives no indication whatsoever of the occurrence of transition between the two series, and so far as it goes the nature of the non-granular cells remains in doubt.

When the histological features of the leucocytes are considered, however, it is found that these cells present perfectly definite myeloid characters: they correspond in every detail with those described in Case II. The only differences recognizable between the blood-pictures in these two cases are the smaller percentage of granular cells here, 3 per cent. in place of 6 per cent., and the less frequent occurrence of definite transition forms such as cells with looser reticulum or with metachromatic violet granules. Absolute proof of the myeloid nature of the case is impossible in absence of histological examination of the blood-forming organs, but the characters of the cells seem too definitely those of Naegeli's myeloblasts to render possible any other explanation. This case would therefore appear to represent a stage of embryonic blood-formation at which the value of Schultze's oxydase reaction as a test for myeloblasts breaks down. But when one remembers the large percentage of negatively-reacting cells present in Case II, which was proved to be myeloid by histological examination, the occurrence of such a stage as this can be recognized as a probability.

Conclusions.

1. The occurrence of a positive indophenol-oxydase reaction in large non-granular cells in acute leukaemia is a certain proof of their myeloid nature, and enables a diagnosis of acute myeloid leukaemia to be readily made from blood-examination.

2. The oxydase reaction is negative in the more embryonic forms of marrow-cells. It is always negative in small myeloblasts, and is probably always negative in the most typical stage of large myeloblasts with uniformly dense basophil reticular protoplasm. When it falls positive in these large non-granular cells it is associated with alterations in the protoplasm which are recognizable by ordinary staining methods, and which indicate stages of ripening towards the granular myelocytes.

3. Cases of acute myeloid leukaemia may occur in which the type of blood-formation is so embryonic that the oxydase reaction is valueless for differential diagnosis, but even in such cases the histological characters of the large leucocytes may render a diagnosis possible.

I have to acknowledge my indebtedness to Professor Samson Gemmell and Dr. Barclay Ness for the use of clinical data for Cases I and II, and to Professor Muir for the pathological material in these cases.

REFERENCES.

1. Browning, *Lancet*, Lond., 1905, ii. 507.
2. Butterfield, *Deutsch. Arch. f. klin. Med.*, 1908, xcii. 336.
3. Butterfield, Heineke and Meyer, *Fol. Haem.*, 1909, viii. 325.
4. Dunn, *Journ. Path. and Bact.*, Camb. and Lond., 1910, xv. 20.
5. Ehrlich, *Diseases of the Blood* (Eng. Trans.), Lond., 1905, 544.
6. Fabian, Naegeli und Schatiloff, *Virch. Arch. f. path. Anat.*, 1907, cxc. 436, Case 10.
7. Graetz, *Beitr. path. Anat. u. allg. Path.*, Jena, 1910, xlix. 338, Case 3.
8. Isaac and Cobliner, *Fol. Haem.*, x. 459.
9. Kahn, *Frankf. Zeit. f. Path.*, ix. 259.
10. Marchand, *Münch. med. Woch.*, 1911, lviii, i. 924.
11. Marchand, ibid., 1911, 1215.
12. Meyer und Heineke, *Deutsch. Arch. f. klin. Med.*, 1907, lxxxiii. 435, Case 17.
13. Naegeli, *Deutsch. Arch. f. klin. Med.*, 1900, lxvii. 279.
14. Naegeli, *Blutkrankheiten und Blutdiagnostik*, Leipz., 1912, 173.
15. Pappenheim and Hirschfeld, *Fol. Haem.*, v. 347, Case 1.
16. Pappenheim, *Prolegomena*, *Fol. Haem.*, xi. 1.
17. Peters, *Münch. med. Woch.*, 1909, lvi, ii. 1478.
18. Schultze, *Beitr. path. Anat. u. allg. Path.*, Jena, 1906, xxxix. 252.
19. Schultze, *Münch. med. Woch.*, 1909, lvi, i. 167.
20. Scott, *Lancet*, Lond., 1907, ii. 1527.
21. Thomas, *Zeitsch. f. klin. Med.*, Berlin, 1911, lxxiii. 308.

EXPLANATION OF FIGURES.

PLATE 16, FIG. 1. Case I. *Blood-film*: oxydase reaction. The polymorphonuclear leucocyte near the centre gives an intense reaction. The other cells are stained with varying degrees of intensity: in two there is no reaction. × 500.

FIG. 2. Case I. *Bone-marrow*: oxydase reaction. The round clear areas are the diminished fat-cells. The pale areas are clumps of more embryonic myeloblasts. × 50.

FIG. 3. Case I. *Spleen*: oxydase reaction. Intense in almost all the cells in the pulp. Negative in the remains of the lymph-follicles. × 50.

FIG. 4. Case I. *Liver*: oxydase reaction. Intense in leukaemic infiltrations in portal tracts. × 50.

FIG. 5. Case I. *Kidney*: oxydase reaction. Indicates the distribution of myeloid cells in the connective-tissue. × 50.

PLATE 17, FIG. 6. Case I. *Section of small cervical lymphatic gland*: oxydase reaction. Pulp full of myeloid cells. Remains of lymph-follicles unstained. × 50.
(Sections 2–7 cut by paraffin process.)

FIG. 7. Case II. *Blood-film*: Jenner's stain, to show nucleoli 3–4, in myeloblasts. × 500.

FIG. 8. Case II. *Blood-film*: oxydase reaction. Positive in one polymorphonuclear and in a ripening myeloblast: negative in three other myeloblasts. × 500.

FIG. 9. Case II. *Liver*: Portal tract with leukaemic infiltration. Haemalum and eosin. × 100.

FIG. 10. Case II. *Liver*: oxydase reaction in fairly large proportion of cells forming a collection in a portal tract. Frozen section. × 100.

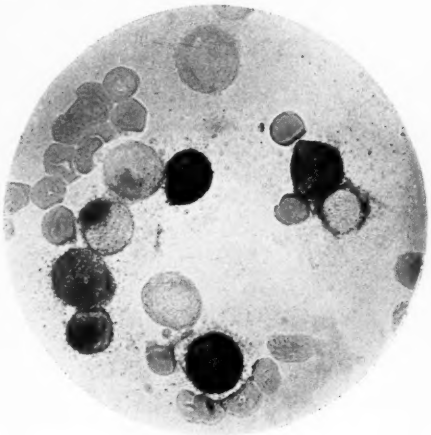


FIG. 1

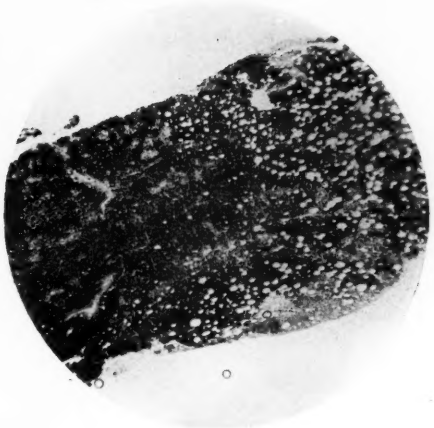


FIG. 2

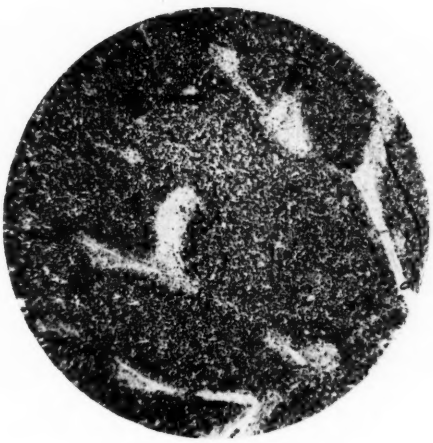


FIG. 3

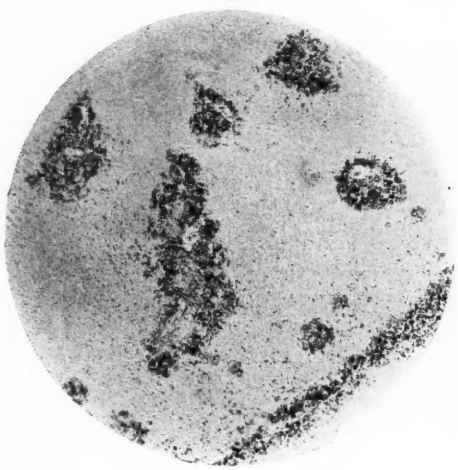


FIG. 4



FIG. 5



FIG. 6

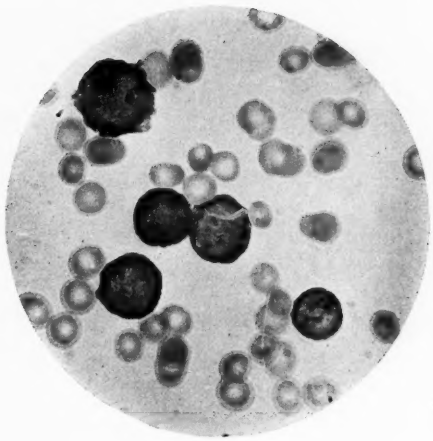


FIG. 7

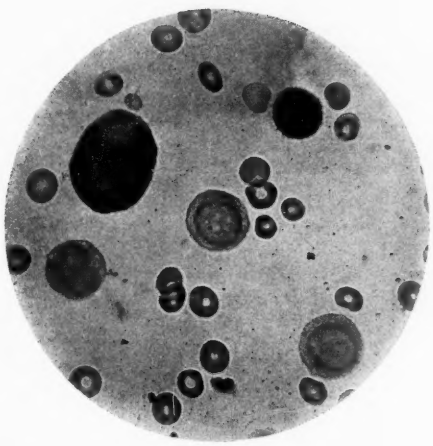


FIG. 8

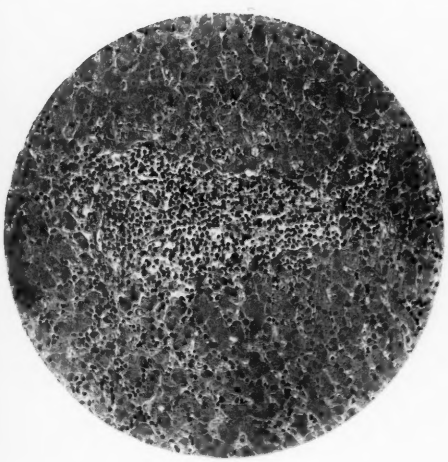


FIG. 9

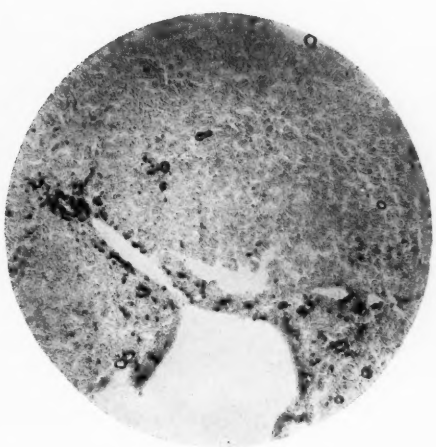


FIG. 10



INVESTIGATIONS ON THE GASTRIC JUICE IN MALIGNANT AND NON-MALIGNANT DISEASES OF THE STOMACH AND DUODENUM

PARTS II, III, AND IV [1]

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[1] Part I of these Investigations appeared in Vol. vi, p. 71 of this Journal, October, 1912.

Part II. The Chemical Interpretation of the Results of Gastric Analysis.

Introduction.

In spite of the mass of literature on the chloride secretion of the gastric juice, there yet remain considerable gaps in our knowledge of the subject. Some of these we have endeavoured to fill in the following pages. The work here described deals with the *chemical* interpretation of the results of analysis, while in Part III we shall consider the *pathological* significance of our results, reserving *clinical* deductions for Part IV.

The main investigations have been made on chloride secretion, but for this purpose it has been found necessary to investigate also the relationship of peptic activity to other functions. In order to do this, advantage has been taken of the method for the quantitative estimation of peptic power recently elaborated by Fuld and Levison and described by us in some detail in these pages.[2] While this work has been in progress one of us (C. S.) has checked our conclusions by animal experimentation, but as this part of the work is still incomplete we do not for the present dwell upon it.

(*a*) *Methods.* Although many methods have been employed for the analysis of gastric juice (35), no absolutely satisfactory procedure has yet been evolved. The difficulty arises from the complexity of the mixture that goes to make up a digested or partially digested test-meal. It has long been recognized that in this mixture chlorine may be found in three separate forms, viz. as free hydrochloric acid, as sodium chloride, and as the hydrochloride of organic substances, but the methods for estimating these three forms are still no more than approximately correct.

The estimation of the *total chloride* presents no obstacles and can be readily made by Volhard's method, but the processes available for separating this total into its component factors are less satisfactory. We have ourselves estimated acidity by titration with dimethylaminoazobenzene[3] (orange G, Töpfer's reagent), as well as by phenolphthalein, and we have also determined the amount of inorganic chloride present by the Volhard-Lüttke (15) method recommended by Willcox (34), i. e. by estimating the chloride remaining in a measured quantity of gastric juice after incineration. In this latter procedure the free hydrochloric acid as well as the hydrochloric acid in combination with organic bases is volatilized during the charring process, leaving only the inorganic chloride. The secreted chloride ('active chloride', as Willcox prefers to call it) is estimated by subtracting this inorganic chloride that remains in the

[2] See this Journal, Vol. vi, pp. 71–81, with Bibliographical References.

[3] This titration value is referred to henceforth as the *dimethyl acidity*.

ash from the total chloride.[4] Finally, we have in each case estimated also the amount of nitrogen present.

(*b*) *On certain sources of error in analysis.* Methods of titration (e.g. dimethyl) as well as the Volhard-Lüttke process have frequently been used for estimating chlorides. The former has been supposed to determine the so-called 'free hydrochloric acid', and the latter the 'secreted chloride'. Both processes, however, contain sources of error and confusion. In the first place, the hydrochlorides of amino-acids, of peptones, and of other similar substances act as acids. These substances are products of digestion, and therefore contained in all natural juices withdrawn after a test-meal. The relationship between so-called 'free hydrochloric acid' (as estimated by dimethyl) and these hydrochlorides is very definite and is considered in the following sections (*c* and *d*).

Secondly, the acids of the type of lactic, butyric, and acetic may be present, and are not entirely without effect upon indicators. There is no method that can be adapted for clinical purposes of detecting small amounts of these substances quantitatively, but our general observations support those of Panton and Tidy (21), that the occurrence of these acids in appreciable quantities is comparatively rare and that the error due to them is usually very small.

Thirdly, the method of estimating the chloride present as sodium chloride contains a much more serious source of error, due chiefly to the presence of phosphates in the ash. If acid phosphates (of the type Na_2HPO_4 and NaH_2PO_4) be present, these will react with sodium chloride in accordance with the equations —

$$Na_2HPO_4 + NaCl = Na_3PO_4 + HCl$$
$$NaH_2PO_4 + 2NaCl = Na_3PO_4 + 2HCl.$$

We have made a number of estimations of phosphorus in gastric juices and have invariably found that practically the whole is in organic combination (since it cannot be precipitated by ammonium magnesium citrate[5]). The phosphorus does not appear, therefore, to be secreted as phosphate by the stomach, and is probably present in the form in which it exists in the food. To confirm this conclusion we have estimated both nitrogen and phosphorus in a number of cases, and have found these two factors to vary in roughly parallel fashion.[6] We

[4] It is usually assumed (as we have done in the following pages) that the inorganic chloride present in gastric juice is of no special significance, and is derived either from neutralization of the secreted hydrochloric acid, or from the test-meal itself, or by a process of simple osmosis. G. Graham, however, has recently attached greater significance to this element (9), and one of us (C. S.) is engaged on an experimental investigation which tends to show that part, at least, of this inorganic chloride may be of the nature of an active secretion.

[5] In control analyses to which a known amount of inorganic phosphate had been added, we were able to precipitate it quantitatively by this reagent: see Mathieson (17).

[6] We give below a series of twenty estimations of nitrogen and phosphorus—the latter determined by Neumann's method. The numbers for nitrogen represent the number of cubic centimetres of $\frac{N}{10}$ NaOH required to neutralize the ammonia produced by Kjeldahlizing 10 c.c.

do not, therefore, attach any pathological or physiological significance to the phosphorus content, though its effect on the actual results of analysis may be appreciable.

During incineration the phosphorus is converted into the inorganic phosphate, and its influence on the analytical results will depend upon the amounts existing in the ash either as Na_3HPO_4, Na_2HPO_4, or NaH_2PO_4, or as the corresponding salts of other metals. The reaction of the two latter phosphates with the sodium chloride present leads to the formation of free hydrochloric acid during incineration, and will always make the readings of inorganic chloride too low, and the estimation of secreted chlorides obtained by difference (i.e. total chloride *minus* inorganic chloride) correspondingly too high. Thus in our hands the 'secreted' (active) chloride has usually given readings of about 1·0 c.c. higher than the total acidity, nor is this difficulty removed by adopting the suggestion of Willcox (35) and estimating the total chloride in gastric juice rendered alkaline by addition of sodium carbonate.

Attempts have been made to obviate the errors due to this phosphorus factor. Sjöqvist (30), for example, treats the gastric juice with barium carbonate, to convert the free and organically combined chloride into barium chloride. He then determines this chloride indirectly by estimating the barium in the filtrate from the excess of carbonate after destruction of the organic matter by incineration. We have found, however, from experiments carried out with artificial gastric juices of known composition that the process is far from satisfactory, and does not yield such good results as those obtained by the Volhard-Lüttke method. Our conclusions on this point have been confirmed by Mlle van Herwerden and W. S. Ringer in their work on the gastric activity of Elasmobranch fish (11).

Fourthly and lastly, another source of error may be briefly considered. The nitrogenous products of digestion contain in themselves *amphoteric* substances of the nature of amino and carboxyl groupings. These become a more serious source of error in those gastric juices which contain a high proportion of peptone.

(*c*) *On the difference between the 'total acidity' and the acidity attributed to 'free hydrochloric acid'.* But even if the analytical methods be accepted as

of the juice. The numbers for phosphorus represent the equivalent of $\frac{N}{10}$ NaOH for the phosphomolybdate precipitated from 10 c.c. of juice.

	N.	P.		N.	P.
1	4·3	3·7	11	10·8	9·1
2	9·3	11·6	12	8·1	8·8
3	10·9	9·2	13	9·2	7·2
4	7·2	5·7	14	12·8	16·5
5	7·6	5·0	15	9·0	9·3
6	7·8	7·2	16	16·3	22·0
7	7·0	5·0	17	9·4	9·3
8	10·6	12·2	18	10·5	9·0
9	7·2	4·2	19	3·5	4·8
10	9·4	10·2	20	4·5	6·9

sufficiently accurate, the chemical interpretation of the results has hitherto seemed by no means clear. The chief source of confusion has been the difference of the titration values of gastric juices to different indicators, as, for instance, to phenolphthalein and dimethyl.

It is unnecessary to discuss here the theory of indicators, which has been placed on an exact basis by the use of the hydrogen electrode in the hands specially of Friedenthal (8) and Salm (24 and 25). The whole subject in its biological aspect has recently been exhaustively summarized by Sörensen (31) in a valuable monograph,[7] while the special action of indicators in gastric juice has been investigated by Panton and Tidy (21). Their work, as well as our own experiments, demonstrates the value of dimethyl and phenolphthalein acidity as rough indices of gastric activity. In order to make clear, however, the relationship between these two chemical factors, viz. dimethyl acidity and phenolphthalein acidity, it is necessary to consider the behaviour of hydrochloric acid in the presence of proteins and their degradation products, substances which are necessarily its invariable companions in any specimen of gastric juice.

As we have pointed out in our previous paper (pp. 72 and 73 of the present volume), a protein is essentially a polypeptide, and during the course of digestion it undergoes hydrolysis, thus yielding other polypeptides and amino-acids, which become less and less complex as the process continues. The effect is thus to increase the *number* of acid reactive amino-groups. Thus, if glycylglycine, the simplest known polypeptide, be taken as an example, this degradation process can be represented as follows:

$$CH_2(NH_2)CO\cdot N\cdot H\cdot CH_2\cdot COOH + H_2O = 2CH(NH_2)\cdot COOH.$$

From this equation it will be seen that one molecule of glycylglycine containing one amino-group undergoes scission into two molecules of glycine (glycocol) containing two amino-groups; the former combines with one molecular equivalent of hydrochloric acid, whereas the latter combines with twice this amount. The same reasoning applies in the case of a complex polypeptide or protein which may be represented by the general formula of the type:

$$\begin{matrix} R & & R' & & R'' & & Rn \\ C\cdot(NH)_2—CO\cdot NH\cdot C\cdot CO\cdot NH\cdot C\cdot CO—NH\ldots C\cdot COOH, \end{matrix}$$

where R represents a hydrogen atom or any radicle, which is found in an amino-acid derived from the hydrolysis of a protein. For every peptide group (—CO—NH—) which undergoes hydrolysis during digestion, an amino-carboxylic acid group is set free (—CO—NH— + H_2O =—COOH NH_2—). Thus as a protein undergoes digestion, the number of amino-groups increases, and the capacity for combination with hydrochloric acid therefore also increases.[8] With

[7] This work is usefully abstracted in a recent paper by G. S. Walpole (33).

[8] Free hydrochloric acid accelerates the hydrolysis of proteins. Methods for estimating the free hydrochloric acid in gastric juice have been suggested which consist in determining the rate of inversion of cane-sugar or of methylacetate when the reagents are incubated with the juice (Moore (19)). The more uncombined hydrochloric acid present, the greater will be the rate at which such chemical changes will take place. These methods contain an inherent

this increase in combining power, the titration value of any mineral acid present becomes altered.

As a type of hydrochloride of a digestion product, that of glycine may again be taken. The hydrochloride of this substance is represented by the formula $HCl \cdot NH_2 \cdot CH_2 \cdot COOH$, and such a product as this reacts as an acid to phenolphthalein and dimethyl. The titration values, however, of such a hydrochloride to these two indicators are very different. Indeed, owing to the amphoteric character of glycine and of other amino-acids and polypeptides, somewhat complex phenomena are observed when hydrochlorides of such substances are neutralized by alkaline solutions in the presence of various indicators.

Thus, if hydrochloric acid be mixed with the chemical equivalent of glycine and be titrated with sodium hydroxide, it will be found that if phenolphthalein is used as an indicator, more alkali will be required for neutralization than if the hydrochloric acid were titrated without the glycine, while on the other hand if dimethyl is used as an indicator, less alkali will be needed than for titration without the glycine. The greater the proportion of glycine added, the greater will be the alteration in the titration values to these two indicators, and the difference varies in approximate proportion to the amount of glycine present. This point is illustrated in Table I. 5 c.c. of $\frac{N}{10}$ hydrochloric acid were diluted to 50 c.c. with water containing varying amounts of glycine,[9] and the titration values to dimethyl and phenolphthalein ascertained.

TABLE I.

Titration values of 5 c.c. $\frac{N}{10}$ HCl in the presence of increasing amounts of glycine.

A. Nitrogen equivalent expressed as number of c.c. of $\frac{N}{10}$ H_2SO_4 needed to neutralize NH_3 produced by Kjeldahlization.[10]	B. Number of c.c. of $\frac{N}{10}$ NaOH needed to neutralize to dimethyl.	C. Number of c.c. of $\frac{N}{10}$ NaOH needed to neutralize to phenolphthalein.	'Nitrogen factor' $\frac{C-B}{A} \times 10$.
10	4·4	5·3	0·9
20	3·8	5·6	0·9
30	3·1	5·8	0·9
40	2·8	6·0	0·8
50	2·6	6·4	0·8

The experiments epitomized in this table illustrate a point which is encountered also in the *clinical* examination of gastric juice, viz. that the greater

source of error, in that the peptones in the gastric juice also undergo hydrolysis, and the combining capacity of the hydrolysed product is greater than that of the original juice. Hence, at the end of the operation, the amount of uncombined hydrochloric acid present is less than at the beginning, and the rate of hydrolyses of cane-sugar or methyl acetate progressively decreases. For this reason, all results obtained by 'catalysis methods' for estimating hydrochloric acid are too low.

[9] As we do not here consider the theory of indicators, we have purposely adopted an empirical method in dealing with these experiments.

[10] i.e. 10 c.c. N/10 H_2SO_4=10 c.c. N/10 glycine solution.

the amount of digestion product present, the greater the difference between the dimethyl and the phenolphthalein titration values. The experiments illustrate, however, another point which cannot be here numerically recorded, but which is also of clinical importance (and has been briefly referred to on p. 312 as a possible source of error), viz. that as the amount of glycine (or digestion product) is raised, the titration-end point becomes less and less definite, owing to the increase in the amount of amphoteric amino and carboxyl substance.

(*d*) *The special action of digestion products on titration values of gastric juices.* From the above discussion (in section *c*) and Table it will be observed that the difference between the titration value with phenolphthalein and that with dimethyl is proportional to the amount of nitrogen present in any given solution of an amino-acid or mixture of amino-acids. In other words, if C represent the phenol titration, B the dimethyl titration, and A the nitrogen equivalent, $\frac{C-B}{A}$ is a constant. We propose to designate this figure multiplied by 10 as the *nitrogen factor*. Now since the product of peptonization may be regarded as a mixture of amino-acids, the nitrogen factor for any digest should be a constant within the limits of experimental error, and this in fact we have found to be the case. Thus, we have ourselves determined it in the case of commercial Witte's peptone and of gluten peptone.[11] The titration results to these two substances are indicated in the following Tables (II and III) and chart.

TABLE II.

Titration values of 5 c.c. $\frac{N}{10}$ HCl diluted to 10 c.c. with water containing increasing quantities of Witte's peptone.

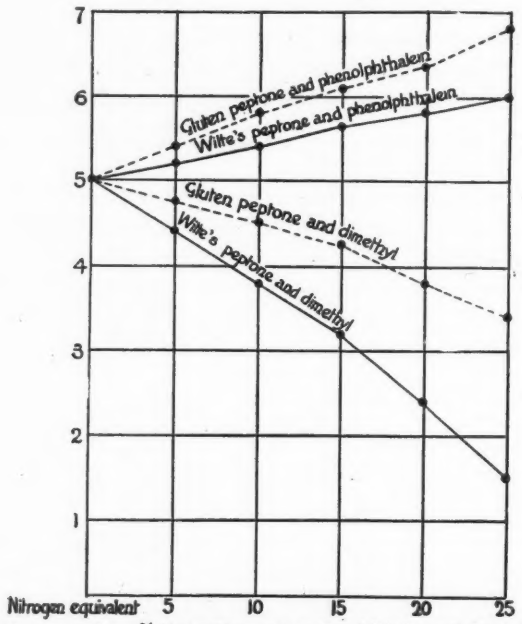
A. Nitrogen equivalent.	B. Titration with dimethyl.	C. Titration with phenolphthalein.	Nitrogen factor $\frac{C-B}{A} \times 10$.
5	4·40	5·20	1·6
10	3·80	5·40	1·6
15	3·20	5·65	1·6
20	2·40	5·80	1·7
25	1·55	5·95	1·7

[11] Gluten peptone was prepared as follows: Wheaten flour was freed from carbohydrate as completely as possible by kneading. The gluten thus obtained was digested with pepsin in the presence of 3/20 N sulphuric acid for several days, toluene being added to keep the mixture (which was shaken from time to time) aseptic. The sulphuric acid was then quantitatively removed by barium hydroxide. Finally the filtrate, which contained excess neither of sulphuric acid nor of barium, was evaporated to a small bulk *in vacuo*. The nitrogen was estimated in this liquid, which was directly used for experiment. In the experiments on Witte's peptone a filtered solution of the ordinary commercial preparation was employed.

TABLE III.

Titration values of 5 c.c. $\frac{N}{10}$ HCl diluted to 10 c.c. with water containing increasing quantities of gluten peptone.

A. Nitrogen equivalent.	B. Titration with dimethyl.	C. Titration with phenolphthalein.	Nitrogen factor $\frac{C-B}{A} \times 10$.
5	4·75	5·45	1·4
10	4·50	5·80	1·3
15	4·20	6·10	1·3
20	3·75	6·35	1·3
25	3·45	6·80	1·3



Titration values of 5 c.c. $\frac{N}{10}$ Hydrochloric acid to phenolphthalein and dimethyl in presence of Witte's peptone (continuous line) and Gluten peptone (broken line).

It will be observed from the last columns of Tables I, II, and III that the nitrogen factor is a constant for any particular amino-acid (e.g. glycine, Table I) or mixture containing amino-acids and peptides (e.g. peptone, Tables II and III). A further set of experiments was made to ascertain how the titration numbers and nitrogen factor varied during the process of digestion of gluten. For this purpose 2·5 grammes of gluten were suspended in 500 c.c. $\frac{N}{10}$ hydrochloric acid, and a commercial preparation of pepsin was added in such quantity that the strength was about that of an average gastric juice (50 units). The mixture was warmed to 37° before addition of the pepsin, and was then incubated. Samples were withdrawn from time to time and analysed. The results are indicated in the following table. For the study of such changes as are here set forth gluten is particularly convenient, as the undigested protein is only slightly soluble in dilute acids.

TABLE IV.

Titration values of 5 c.c. of gluten digest in $\frac{N}{10}$ HCl containing pepsin equivalent to a peptic index of 50 withdrawn at various times.

Time of incubation in minutes.	A. Nitrogen equivalent.	B. Titration with dimethyl.	C. Titration with phenolphthalein.	Nitrogen factor $\frac{C-B}{A} \times 10$.
0	2·3	4·80	5·30	2·2
30	4·9	3·80	4·90	2·2
60	9·5	3·15	4·80	1·7
90	13·7	2·75	4·90	1·6
120	18·9	2·12	5·15	1·6
150	22·7	1·87	5·30	1·5

It will be noted in this table that the nitrogen factor forms a continuously descending series. The changes, moreover, in the titration values do not quite form a linear function. This phenomenon is in accord with ascertained facts as to the nature of indicators (8, 24, and 31).

Comparison may now be made between the nitrogen factor in such artificial digests as are displayed in Table IV, and the nitrogen factor of the gastric juice removed after the standard test-meal.[12] The results of a number of cases, indiscriminately chosen, are given in Table V. Cases, however, are neglected which are alkaline to dimethyl[13] (and which therefore contain no free hydrochloric acid) or which have a peptic index below 10 (and therefore have little or no digestive activity).

TABLE V.

Nitrogen equivalent, titration values, and nitrogen factor in 20 cases of normal human gastric juice indiscriminately chosen to illustrate the relative constancy of the nitrogen factor.

	A. Nitrogen equivalent.	B. Titration to dimethyl.	C. Titration to phenolphthalein.	Nitrogen factor $\frac{C-B}{A} \times 10$.
1	12·2	2·7	5·6	2·4
2	13·1	1·9	5·4	2·5
3	9·7	3·0	5·4	2·5
4	13·0	0·9	4·0	2·4
5	17·3	1·7	5·7	2·3
6	8·0	2·5	4·7	2·7
7	9·4	5·6	8·4	2·8
8	7·7	2·4	4·4	2·6
9	12·1	1·7	4·7	2·5
10	12·2	1·9	5·1	2·6
11	13·0	0·5	4·0	2·8
12	12·3	2·6	5·6	2·6
13	15·8	1·2	5·2	2·5
14	6·0	0·3	1·9	2·7
15	4·3	4·3	5·3	2·7
16	9·3	4·5	7·7	2·8
17	10·0	1·7	4·1	2·4
18	7·3	4·8	6·8	2·7
19	7·6	5·4	7·2	2·4
20	7·9	1·9	3·9	2·5

[12] The standard test-meal was two rounds of buttered toast and a pint of weak tea with milk and sugar. The meal was removed one hour after ingestion.

[13] In cases which are alkaline to dimethyl the turning-point can of course be determined by titrating with acid, but as such gastric juices are usually without any appreciable peptic activity (as we show in Part III, p. 327) we have neglected them here.

It will be seen from Table V that in the majority of cases the nitrogen factor varies only slightly from a constant 2·5, which figure, indeed, it approaches closely in the most active juices. This constant is higher than the nitrogen factor in the artificial gluten digests. It thus seemed conceivable that hydrochloric acid might be secreted in the stomach in some loosely combined form. An examination of an artificial digest of minced buttered toast and tea was therefore made (Table VI) under exactly the same conditions as described in the experiment for the gluten digest, the results of which are detailed in Table IV. The nitrogen factor obtained approximated closely to that of natural gastric juice. The difference between the nitrogen factor of the gluten digest and that of a test-meal is therefore probably due to the bases in the tea.

TABLE VI.

Nitrogen equivalent, titration values, and nitrogen factor of a digest of minced buttered toast and tea, to which had been added an equivalent of $\frac{N}{20}$ HCl and pepsin to an index of about 50.

Time of incubation in minutes.	A. Nitrogen equivalent.	B. Titration to dimethyl.	C. Titration to phenolphthalein.	Nitrogen factor $\frac{C-B}{A} \times 10$.
0	3·9	3·2	5·4	5·6
30	7·8	2·9	5·5	3·3
60	12·0	2·6	5·7	2·6
90	13·4	2·5	5·9	2·5
120	14·2	2·5	6·0	2·5

The approximation of the nitrogen factor of the artificial digest (2·6–2·5) to the nitrogen factor obtained from gastric juice (2·4–2·5) makes it unlikely that hydrochloric acid is secreted in any other than the free mineral form, though some of the acid passes into organic combination as soon as secreted. This conclusion is further emphasized by the experiments of one of us (C. S.) on living animals. The stomach of an anaesthetized cat was well washed out and then left full of distilled water. A hormone was injected into a vein, and after an hour the gastric contents were withdrawn and examined.[14] Considerable secretion of hydrochloric acid was thus obtained (as much as a total of 30 c.c. $\frac{N}{10}$ HCl in one animal), but the titration values to dimethyl and phenolphthalein were almost identical in each case. This was true whatever the hormone used (extract of cat's pylorus, bouillon or peptone) and whether the vagi were severed or not. If, however, digestion products were allowed to remain in the stomach or if the juice became mixed with blood, the phenol and dimethyl readings were found to differ.

It will thus be seen that in estimating the acidity of gastric juice to indicators, the amount of nitrogen present must be taken into account, and that the nitrogen factor is a useful aid in determining digestive activity. This factor

[14] A procedure similar to that we have adopted was described by J. S. Edkins (5 and 6).

is likely to be high when digestion is slight, either owing to the lowness of peptic power or to inadequate chloride secretion. It is, moreover, likely to be high when test-meals are prematurely withdrawn before the standard time (one hour). In healthy and active cases, however, as well as in hyperactive cases, the nitrogen factor settles down to a figure closely approximating to 2·4 or 2·5 and only occasionally a little lower (2·2–2·4).

(*e*) *The Günzburg reaction.* Much stress has been laid by some writers on the delicacy of Günzburg's reaction, and in simple solutions in water it is possible to detect one part of acid in ten thousand by this means. Clinically, however, owing to the mixture of substances present, the test by no means shows such extreme delicacy. As a rule, when the Günzburg reaction is negative, a juice is also alkaline to dimethyl, but this is by no means invariably the case. In a series of artificial mixtures of varying amounts of acid and peptone, it has always been possible to prepare mixtures distinctly acid to methyl orange and yet giving a negative result with Günzburg's test.[15] This statement is illustrated in the following table:

TABLE VII.

To illustrate the relationship between Günzburg's reaction and dimethyl values in the presence of varying quantities of peptone.

Nitrogen equivalent of 10 c.c.	No. of c.c. $\frac{N}{10}$ HCl in 10 c.c.	Titration value to dimethyl of 10 c.c.	Günzburg's reaction.
5	1	0·75	very faint
5	2	1·75	+ +
10	1	0·50	−
10	2	1·50	+
15	1	0·25	−
15	2	1·20	−
15	3	2·25	+
20	1	0·0	−
20	2	0·75	−
20	3	1·80	very faint
20	4	2·80	+

The influence of nitrogenous digestion products on Günzburg's reaction is well marked. We have not, however, elicited for Günzburg's test so definite a relationship to the nitrogen content as that which we have succeeded in tracing for dimethyl. Since heat is employed in carrying out Günzburg's test and the consequent hydrolysis of peptones may diminish the amount of uncombined hydrochloric acid present, we prefer to use the dimethyl reaction as a basis of differentiating gastric juices.

[15] The name of Günzburg is frequently attached to a test that is not quite that of its eponymic author. We have applied the test in the form originally suggested by Günzburg (10) and adopted by Ewald (7).

In a series of articles on the value of indicators in the examination of gastric juice Christiansen (4) has very recently pointed out that the Günzburg reaction is dependent on the acid present and not upon concentration of hydrogen ions.

Part III. The Pathological Significance of the Results of Gastric Analysis.

Introduction.

In considering the pathological significance of the chemical composition of gastric juices, attempts have been frequently made to devise a method of classification. Any such process must be of its nature more or less arbitrary, and the analyses of one class shade almost imperceptibly into those of another. The data available for classification have already been described in Part II (pp. 310–311) of these investigations. We may proceed therefore to discuss in detail the bearings of analytical results on pathological conditions, and their consequent utility as a basis of classification.

(*a*) *Acidity to indicators* may be detected by the Günzburg test or by dimethyl titration. As previously explained (Part II, section *e*), we consider that in the majority of cases dimethyl is the more valuable test. It has also the advantage of easy quantitative application. We shall therefore regard the dimethyl readings as yielding an indication of the amount of 'free hydrochloric acid' present.

Although the term 'free hydrochloric acid' is constantly employed in reference to certain reactions of gastric juice, it is by no means an accurate designation. When amino-acids or other digestion products are mixed with their molecular equivalent of hydrochloric acid, a solution acid to dimethyl is obtained. The equilibrium conditions in such a mixture are somewhat complex and an acid reaction to dimethyl (or to any other indicator) merely implies that the hydrogen ion concentration has reached a certain limit. *The term 'free hydrochloric acid' can therefore be used in such cases in only a conventionalized sense* to indicate a certain degree of acidity, and in this sense we use the term in the following pages. Both the dimethyl test and the Günzburg reaction are then indicators of a degree of hydrogen ion concentration, and of the two we consider the dimethyl test (for reasons already stated) to be the more reliable criterion.

Now it is *a priori* conceivable that the absence of dimethyl acidity may be due to one of two causes:

1. Hydrochloric acid, though secreted, may be so combined with amino-acid groups that hydrogen ion concentration is reduced below the limit needed for a positive reaction to dimethyl. In such a case should the amount of secreted chloride approach the normal we may expect an exceptionally large quantity of nitrogenous digestion products, since only by combination with these can the hydrogen ion concentration be reduced.

2. The glands of the stomach may have altogether ceased to secrete hydrochloric acid. In such a case (achylia) we should expect to find low total chlorides, an absence of combined chloride, and—since the digestive power will be nil—only a small amount of dissolved nitrogenous substance.

Of course an intermediate state between (1) and (2) is possible, and is

indeed frequently encountered. In such a condition, which may be the result of stasis, the secretion of chloride is below normal, and a considerable amount of dissolved nitrogenous substance is delayed in the gastric juice. Thus all the hydrochloric acid present is so completely combined with basic groups in the dissolved nitrogenous products, that the reactions of free mineral acid are no longer in evidence.

Cases of this kind are exceedingly common, and a typical history may be briefly recounted. The patient was a thin, dyspeptic, nervous woman, aged 35, the overworked mother of several children. She had long suffered from vague gastric pain after food, and from a sense of weight and distension in the abdomen. The right kidney was very obviously mobile. For some months the patient had been getting thinner and clearly going downhill. The analysis of the gastric contents gave the following results:

Phenolphthalein acidity	4·4
Dimethyl acidity	0·0
Günzburg's test	negative
Peptic index	13
Total chloride	7·4
Secreted chloride	5·8
Nitrogen	12·8
Nitrogen factor	3·5

The patient was kept for three days in bed, with no other treatment than simple purgatives. During this period the stomach-wall regained its tone, stasis was diminished, the amount of dimethyl acidity became appreciable, and the peptic index improved while the nitrogen factor fell to normal. The chloride secretion remained practically unaltered and the analysis yielded the following results:

Phenolphthalein acidity	5·2
Dimethyl acidity	1·3
Günzburg's test	positive
Peptic index	50
Total chloride	8·0
Secreted chloride	6·4
Nitrogen	14·2
Nitrogen factor	2·5

These latter readings are practically those of a normal gastric juice, and the symptoms had now disappeared.

Incidentally the analyses from this case illustrate the value and interest of the nitrogen factor. At first sight it might be concluded that since the amount of nitrogen was about the same before and after treatment,[16] there could have been no more retention of digestion products in the one case than in the other. The nitrogen factor, however, furnishes different evidence, and this evidence is confirmed by a scrutiny of the other analytical data. For in the first instance the peptic index was very low, 13, and the dimethyl reaction was negative, two

[16] There was actually rather less nitrogen before than after treatment, 12·8 : 14·2.

frequent accompaniments of gastric atony. During treatment the peptic index rose to normal, with 1·3 of dimethyl acidity.

In this woman the kidney was tethered, and a course of ordinary medical treatment restored her to health, so that organic disease of the stomach may be excluded. The freedom from permanent gastric disability is further demonstrated by the normal amount of chloride secreted even while the atonic condition was at its worst, when the nitrogen factor had risen to 3·5 and the gastric juice had ceased to be acid to dimethyl or Günzburg. In other cases of our series the process had gone further, and the secreted chloride had begun to diminish. Such cases are on the high road to functional achylia. Cases of the kind we have just detailed make the dimethyl acidity unsuitable as a primary basis of classification.

(*b*) '*Secreted*' *chloride.* Negative reactions to 'free hydrochloric acid' are seen in those with organic disease having low 'total acidity' and those with temporary functional disability and a relatively high 'total acidity'. A number of recent writers, notably Willcox (34 and 35), have laid stress on the 'active' or 'secreted' chloride rather than on the acidity to indicators. This position is physiologically unassailable,[17] although in practice it is not without disadvantages. Not only is the method of estimating secreted chloride comparatively cumbrous, but, as we have shown elsewhere,[18] it involves certain sources of experimental error. Moreover, it does not really separate clinical categories. Thus, for instance, we have encountered a number of cases of malignant growth in the pyloric region in which the secreted chloride was high, while in other cases of the same disease the secreted chloride was very low. Similarly, in early cases of simple atony the secreted chlorides are fairly high, but are much lower in advanced cases. In spite of these grave drawbacks, the secreted chloride remains the most informing *single* factor in gastric analysis and we have adopted it as our primary basis of classification.

(*c*) *Peptic activity.* We have already called attention to the Fuld-Levison method for estimating peptic activity,[19] and we have found the peptic index (i.e. the numerical expression of that activity) to be a valuable subsidiary factor in classification. We may here briefly discuss the varieties of peptic index in the different classes of gastric cases.

In a healthy stomach the figure which we have designated the 'peptic index' is usually somewhere between 40 and 50, and probably does not vary greatly outside these limits. Leaving a margin of 10 on either side of these two numbers, we shall probably not greatly err in saying that an index below 30 or above 60 is always pathological. The *general* rule for variation in the peptic index is that it rises or falls with a rise or fall of chloride-secreting activity. While there are frequent exceptions in which the chloride secretion is relatively higher than the peptic index, the peptic index has very seldom been found relatively higher than the chloride secretion. In other words, while

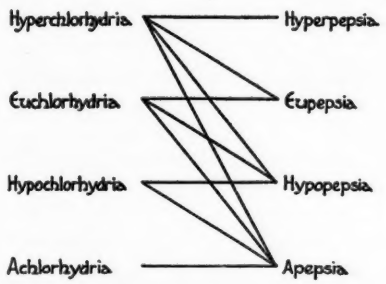
[17] See, however, note 5 to Part II, on p. 311.

[18] In Part II, pp. 311, 312.

[19] In Part I, Vol. vi, pp. 74 and 75.

it is not uncommon to meet cases in which there is much secreted chloride, though the peptic index remains low, we have not come across cases in which there was arrest or great diminution in the output of chlorides with high peptic index. (We return to this point later, in Part IV.)

Combinations observed of hydrochloric acid and pepsin secretion are graphically represented in the following diagram, in which those conditions that have been found in combination are connected by straight lines. Other combinations are only very rarely encountered.[20]



It is thus theoretically possible to divide gastric cases into those in which the peptic index has risen or fallen in parallel with the chloride secretion (combinations represented in the diagram by horizontal lines), and those in which the pepsin is below the relative level suggested by the chloride secretion (combinations represented in the diagram by the more or less obliquely descending lines). In practice, however, there is a good deal of difficulty in making this ideal classification. We have contented ourselves with the two main categories of high and low chloride secretion, each of which is subdivided according to the relative height of the peptic index. Finally, we have reserved for a special group those cases in which secretion has practically ceased (achylia).

These phenomena of pepsin variations seem to indicate that the secretion of pepsin and hydrochloric acid may be controlled by separate mechanisms, and that the pepsin secretion can be influenced independently of the hydrochloric acid secretion. One of us (C. S.) has, in fact, succeeded in experimentally producing in cats a relatively high secretion of acid practically without secretion of pepsin. The mechanism of pepsin secretion is forming the subject of an experimental research.

(*d*) *The 'nitrogen factor'*. We have already dwelt on the meaning and importance of this determination. Theoretically, it is possible by its means to separate those cases in which the digestive power is appreciable into two classes, those in which marked stasis is present and the nitrogen factor is high, and those in which the gastric contents are satisfactorily expelled and the factor is therefore at its normal figure. For the present, however, in this early stage of

[20] The exceptions to this rule are perhaps only encountered in cases of chronic appendicitis presenting gastric symptoms (see Part IV). In such cases a slight comparative elevation of the peptic index has sometimes been observed. See Reference (29).

our knowledge of the subject, we think it best not to complicate the scheme of classification by the introduction of this additional element. We have, therefore, left a column for the nitrogen figures, but have disregarded them in our arrangement of the actual cases.

(*e*) *The double classification by chloride and pepsin secreting activity.* We have thus finally adopted the following provisional chemical classification of gastric juices:

I. With normal and high secretory power.	A. With normal and high peptic power, Table I.
	B. With low peptic power, Table II.
II. With low secretory power.	C. With appreciable peptic power, Table III.
	D. Without appreciable peptic power, Table IV.
	E. Without appreciable secretory or peptic power (achylia), Table V.

We give below the tables corresponding to these categories. For the purpose of this work gastric juice from 300 cases has been examined, but we have excluded all those in which the diagnosis was uncertain (a group comprising doubtless many 'functional' cases), as well as those which do not illustrate any point in the present discussion. In the following tables, therefore, the results are given of only 125 cases.

Table I.

Cases with High or Normal Secretory Activity with High or Normal Peptic Power.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen.	Nitrogen Factor.	Diagnosis.
1	9·6	7·9	+	133	11·4	9·4	7·0	2·4	Duodenal ulcer
2	5·2	1·8	+	100	7·3	6·3	9·2	3·7	" "
3	7·1	4·5	+	100	9·3	7·5	9·3	2·8	" "
4	5·6	3·8	+	100	6·1	4·6	7·5	2·4	" "
5	5·4	1·9	+	95	8·3	5·7	13·0	2·7	" "
6	8·4	5·6	+	91	9·5	7·4	10·4	2·7	" "
7	6·8	4·8	+	73	8·7	6·8	7·2	2·8	" "
8	9·0	7·4	+	67	11·1	6·7	6·4	2·5	" "
9	7·1	5·0	+	67	8·8	6·1	9·0	2·3	" "
10	7·5	5·5	+	60	9·6	6·5	7·7	2·6	" "
11	8·8	7·7	+	50	9·2	6·8	4·8	2·5	" "
12	9·0	5·8	+	50	10·0	9·4	12·4	2·7	" "
13	7·1	4·1	+	40	9·4	8·4	11·8	2·5	" "
14	6·9	4·7	+	40	8·7	7·9	8·3	2·6	" "
15	6·3	1·7	+	40	9·1	7·3			" "
16	7·7	4·3	+	40	9·6	7·4	10·0	3·4	" "
17	6·6	4·1	+	33	9·4	6·7	9·5	2·6	" "
18	11·4	9·2	+	119	15·1	11·3	9·4	2·3	Pyloric ulcer
19	6·8	3·4	+	100	7·3	6·5	14·3	2·4	" "
20	7·1	5·4	+	82	8·4	5·4	7·6	2·3	" "
21	5·7	1·7	+	70	8·1	6·5	17·3	2·4	" "
22	5·9	3·8	+	66	7·3	5·8	7·8	2·7	" "
23	6·4	3·8	+	57	9·4	6·8	10·5	2·5	" "
24	6·9	4·1	+	50	8·4	7·1	11·8	2·4	" "
25	6·0	3·3	+	40	8·4	6·3			" "
26	6·0	4·4	+	40	9·0	6·0	3·2	5·0	" "
27	6·4	3·8	+	40	8·7	7·5	7·6	3·4	" "
28	5·3	1·7	+	80	6·2	5·3	15·0	2·4	Ulcer of body of stomach
29	6·9	4·3	+	67	8·9	7·4	10·8	2·4	" " "
30	4·4	2·9	+	50	7·0	4·6	7·7	2·6	" " "
31	6·9	4·0	+	50	10·9	6·9	9·4	3·1	Carcinoma of pylorus
32	4·3	2·5	+	50	5·9	5·2	6·2	2·8	" "
33	5·0	2·1	+	40	5·8	5·0			" "
34	7·5	3·6	+	120	9·2	8·2	12·7	3·0	Chronic appendicitis
35	5·1	2·0	+	80	7·4	6·2	12·2	2·6	" "
36	11·1	8·1	+	67	13·1	12·4	11·2	2·7	" "
37	4·0	1·9	+	48	5·4	4·0			Gall-stones
38	5·5	3·3	+	33	9·4	3·2			" "
39	6·3	3·3	+	40	8·0	6·8			Alcoholic gastritis
40	4·8	2·5	+	40	7·0	6·0			Gastroptosis
41	7·7	4·8	+	75	9·3	8·0	10·5	2·8	Functional hyperchylia
42	7·7	5·9	+	67	8·5	7·2	4·5	4·0	" "
43	5·7	3·6	+	67	7·2	6·4			" "
44	5·1	2·5	+	37	7·7	6·3			" "
45	5·6	3·6	+	33	7·4	6·6			" "

TABLE II.

High or Normal Secretion of Chlorides with Low Peptic Power.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen.	Nitrogen Factor.	Diagnosis.
46	4·1	1·9	+	29	5·1	4·4	4·5	5·0	Duodenal ulcer. Extensive adhesions
47	5·9	3·0	+	25	8·9	6·4			Duodenal ulcer. Extensive adhesions
48	5·2	2·5	+	10	7·7	6·3	5·6	4·8	Duodenal ulcer. Extensive adhesions
49	4·8	2·2	+	20	8·8	4·8			Duodenal ulcer (acute) and carcinoma of fundus
50	4·8	1·7	+?	34	8·6	5·8	10·1	3·0	Ulcer of body of stomach
51	5·6	3·5	+	33	5·4	4·0	8·4	2·5	,, ,, ,,
52	5·2	3·0	+	10	6·1	4·5	6·3	3·5	,, ,, ,,
53	6·1	4·7	+	29	9·9	7·1			,, ,, ,,
54	6·2	2·8	+	21	10·7	5·8			,, ,, ,,
55	4·9	2·2	+	22	7·0	5·2	8·1	3·4	Carcinoma of pylorus
56	5·6	2·6	+	10	8·0	5·0	12·0	2·5	,, ,,
57	5·7	2·6	+	29	8·5	7·1	13·6	2·3	,, ,,
58	5·8	3·0	+	29	6·6	5·2			Gall-stones
59	5·0	3·0	+	29	7·7	4·5			,, ,,
60	5·2	2·8	+	16	7·5	6·2	10·5	2·3	,, ,,
61	6·7	4·4	+	30	4·9	3·6			Alcoholic gastritis
62	6·9	3·6	+	28	9·1	6·3	10·9	2·9	,, ,,
63	5·9	4·0	+	16	9·1	6·3			,, ,,
64	5·6	2·8	+	10	6·8	4·6			,, ,,
65	5·0	0·0	−	10	7·9	6·1			,, ,,
66	4·4	2·9	+	37	5·8	4·6	3·5	4·3	Cirrhosis of liver
67	5·4	0·6	−	12	7·0	5·1	13·2	3·6	Gastroptosis
68	6·5	3·5	+	10	6·2	4·9	13·6	2·2	Nephroptosis
69	4·0	0·5	−	31	6·7	5·4	11·3	3·1	Functional disturbance
70	4·8	2·8	+	28	9·6	7·8			,, ,,
71	6·1	3·2	+	22	8·3	7·2			,, ,,
72	7·6	3·7	+	22	6·4	4·9	14·4	2·7	,, ,,
73	7·1	4·1	+	17	8·9	5·9			,, ,,
74	5·3	3·6	+	14	8·0	5·4	7·6	2·3	,, ,,

TABLE III.

Low Secretion of Chlorides with Appreciable Peptic Power.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen.	Nitrogen Factor.	Diagnosis.
75	4·6	2·4	+	21	5·0	3·2	7·2	3·0	Duodenal ulcer. Gastric adhesions
76	3·7	1·4	+	20	5·6	3·8	7·1	3·2	,, ,, ,, ,,
77	2·2	0·0	−	17	4·6	2·8			,, ,, ,, ,,
78	4·0	1·0	−	27	7·0	5·2	12·5	2·4	Ulcer of body of stomach
79	3·5	0·9	−?	27	5·9	4·3	10·4	2·4	,, ,, ,,
80	4·0	0·0	−	20	5·7	4·5	9·3		,, ,, ,,
81	3·9	1·9	+	19	6·6	3·2	7·9	2·5	,, ,, ,,
82	3·8	1·9	+	19	5·2	1·9			,, ,, ,,
83	3·3	1·7	−	19	5·8	5·5			,, ,, ,,
84	3·5	0·7	−	31	5·8	3·3	6·4	4·4	Carcinoma of pylorus
85	2·8	0·6	−	26	5·6	3·5	6·4	3·3	,, ,,
86	0·8	0·0	−	11	1·6	0·6	2·9		,, ,,
87	2·0	1·5	+	29	3·2	2·3			Gastric adhesions. Cholecystitis
88	2·9	0·5	−	19	5·6	4·6	13·7	1·9	Portal obstruction
89	4·4	1·0	−	22	5·5	3·7	10·6	3·4	Nephroptosis
90	4·5	0·0	−	13	7·4	5·8	12·8	3·5	,,

TABLE IV.

Low Secretion of Chlorides with Inappreciable Peptic Power—Peptic Index below 10.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen.	Nitrogen Factor.	Diagnosis.
91	2·3	0·0	–	<10	5·4	3·4			Ulcer of body of stomach
92	2·2	0·0	–	<10	6·2	2·7	7·2		,, ,, ,,
93	2·5	0·0	–	<10	7·1	3·0			,, ,, ,,
94	3·9	1·8	+	<10	7·8	4·4	7·6		Carcinoma of fundus
95	1·8	0·0	–	<10	4·5	2·5			Carcinoma of lesser curve
96	1·2	0·0	–	<10	4·8	1·6			,, ,, ,,
97	1·5	0·0	–	<10	5·3	2·6			,, ,, ,,
98	0·9	0·0	–	<10	3·8	2·6			,, ,, ,,
99	2·5	0·0	–	<10	10·2	3·0			Gastric adhesions
100	1·6	0·0	–	<10	4·6	2·3	7·1		,, ,,
101	1·5	0·7	–?	<10	2·0	1·5	3·8		,, ,,
102	2·8	0·1	–	<10	4·5	2·8	8·8		,, ,,
103	3·4	0·0	–	<10	4·5	2·3			Alcoholic gastritis
104	2·9	0·0	–	<10	5·3	2·8	10·8		,, ,,
105	2·8	0·5	–	<10	4·6	2·9	7·4		Portal obstruction
106	1·5	0·0	–	<10	4·7	2·5	13·4		,, ,,
107	2·1	0·0	–	<10	5·4	3·7	9·4		Nephroptosis
108	2·3	0·0	–	<10	4·6	2·8	8·2		,,
109	2·4	0·5	–	<10	6·9	2·0	6·5		,,
110	2·8	0·0	–	<10	6·6	4·6	4·6		Functional disease

TABLE V.

Cases of Achylia.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen.	Nitrogen Factor.	Diagnosis.
111	0·9	0·0	–	<10	0·8	0·0			Carcinoma of lesser curvature
112	1·4	0·0	–	<10	2·9	1·7			,, ,, ,,
113	0·0	0·0	–	<10	0·9	0·0			,, ,, ,,
114	4·6	0·0	–	<10	5·9	1·2			,, ,, ,,
115	0·7	0·0	–	<10	1·9	0·6			,, ,, ,,
116	1·5	0·0	–	<10	2·5	1·5			,, ,, ,,
117	1·0	0·0	–	<10	3·6	1·0	6·2		,, ,, ,,
118	0·8	0·0	–	<10	2·7	1·1			,, ,, ,,
119	0·4	0·0	–	<10	1·2	0·5			Salts of Tartar poisoning
120	0·8	2·8	–	<10	2·3	1·7	3·6		Visceroptosis
121	1·2	0·0	–	<10	3·2	0·5			,,
122	0·4	0·0	–	<10	3·6	1·4	9·1		Cirrhosis of liver
123	2·0	0·0	–	<10	3·1	0·0	4·9		Functional conditions
124	1·6	0·3	–	<10	2·2	1·7	3·2		,, ,,
125	1·8	0·0	–	<10	2·1	1·0			,, ,,

PART IV. SOME CLINICAL DEDUCTIONS FROM THE RESULTS OF GASTRIC ANALYSIS.

Introduction.

There are no pathognomic signs available in gastric juice. It is true that certain types of juice are characteristic of certain types of disease, but there is no type that is the exclusive or invariable accompaniment of any clinical condition.

We propose to consider *seriatim* a number of different pathological conditions on which systematic gastric analysis helps to throw light. Only chronic conditions are discussed in the present communication.

(*a*) *Duodenal ulcer.* The general characteristics of the analyses made in this condition are well defined, and when these characteristics have been absent, complicating circumstances have been disclosed by the surgical procedures adopted. These points are illustrated by the following table:

TABLE I.

24 Cases of Duodenal Ulcer.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.	Diagnosis.
1	9·6	7·9	+	133	11·4	9·4	2·4	Duodenal ulcer. Uncomplicated
3	7·1	4·5	+	100	9·3	7·5	2·8	" " "
4	5·6	3·8	+	100	6·1	4·6	2·4	" " "
5	5·4	1·9	+	95	8·3	5·7	2·7	" " "
6	8·4	5·6	+	91	9·5	7·4	2·7	" " "
7	6·8	4·8	+	73	8·7	6·8	2·8	" " "
8	9·0	7·4	+	67	11·1	6·7	2·5	" " "
9	7·1	5·0	+	67	8·8	6·1	2·3	" " "
10	7·5	5·5	+	60	9·6	6·5	2·6	" " "
11	8·8	7·7	+	50	9·2	6·8	2·5	" " "
12	9·0	5·8	+	50	10·0	9·4	2·7	" " "
13	7·1	4·1	+	40	9·4	8·4	2·5	" " "
14	6·9	4·7	+	40	8·7	7·9	2·6	" " "
15	6·3	1·7	+	40	9·1	7·3		" " "
17	6·6	4·1	+	33	9·4	6·7	2·6	" " "
2	5·2	1·8	+	100	7·3	6·3	3·7	Duodenal ulcer with obstruction. Chronic appendicitis
16	7·7	4·3	+	40	9·6	7·4	3·4	Duodenal ulcer with obstruction. Chronic appendicitis
46	4·1	1·9	+	29	5·1	4·4	5·0	Duodenal ulcer with gastric adhesions
47	5·9	3·0	+	25	8·9	6·4		" " " "
48	5·2	2·5	+	10	7·7	6·3	4·8	" " " "
75	4·6	2·4	+	21	5·0	3·2	3·0	" " " "
76	3·7	1·4	+	20	5·6	3·8	3·2	" " " "
77	2·0	0·0	−	17	4·6	2·8		" " " "
49	4·8	2·2	+	20	8·8	4·8		Duodenal ulcer with carcinoma of fundus

It will be seen that the uncomplicated cases of duodenal ulcer all showed high secretory activity with a peptic capacity either correspondingly high or only slightly depressed, and a nitrogen factor approaching 2·5. In two cases in which a simple duodenal ulcer had led to some degree of obstruction, the nitrogen factor was raised; and in one of these, as well as in all six cases in which there was a considerable formation of gastric adhesions, the peptic index had been very definitely depressed.

(*b*) *Ulcer of the pyloric part of the stomach.* During the last few years anatomists and radiographers have been accumulating evidence showing that the pyloric part of the stomach is to be regarded as a separate organ from the remaining portion. Edkins, working on physiological lines (5 and 6), has shown that it is the chemical stimulus of digestion products acting on the

pyloric part that excites the secretion of hydrochloric acid. Our analytical results appear to fit in with these physiological conclusions.

The analyses of the gastric juice from cases of pyloric ulcer accord closely with those of duodenal ulcer, and differ widely from ulcerous conditions of other parts of the stomach. Of the ten proven cases of pyloric ulcer of which we have reliable analyses, all present in perhaps an enhanced degree the characteristics ascribed to duodenal cases. In only two, Nos. 26 and 27, was the nitrogen index raised, and in those the ulcerative process had led to stenosis and obstruction, and the stomach was dilated and hypertrophied.

TABLE II.

10 Cases of Pyloric Ulcer.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.	Diagnosis.
18	11·4	9·2	+	119	15·1	11·3	2·3	Pyloric ulcer. Uncomplicated
19	6·8	3·4	+	100	7·3	6·5	2·4	" " "
20	7·1	5·4	+	82	8·4	5·4	2·3	" " "
21	5·7	1·7	+	70	8·1	6·5	2·4	" " "
22	5·9	3·8	+	66	7·3	5·8	2·7	" " "
23	6·4	3·8	+	57	9·4	6·8	2·5	" " "
24	6·9	4·1	+	50	8·4	7·1	2·4	" " "
25	6·0	3·3	+	40	8·4	6·3		" " "
26	6·0	4·4	+	40	9·0	6·0	5·0	Pyloric ulcer with dilatation
27	6·4	3·8	+	40	8·7	7·5	3·4	" " "

The variations of the peptic index in cases of duodenal and of pyloric ulcer is interesting. In cases of duodenal ulcer especially, the index varies from the very highest readings to the minimum number 10. So far as our experience extends, however, a very high peptic index (80 and over) is practically diagnostic of one of the two conditions, for in only one case have we met a greatly raised peptic index without an ulcerous condition of pylorus or duodenum being demonstrated at operation. This exceptional case was one of chronic appendicitis, in which also the nitrogen factor was above normal (Case 34, Part III, Table I). The general question of the changes in the gastric juice in cases of chronic appendicitis is discussed by one of us (C. S.) in a recent publication (29). It may be here explained, however, that in cases of chronic appendicitis relatively higher peptic indices were encountered than in any other type of disease that we have examined.

(c) *Gastric ulcer elsewhere than at the pylorus.* Chronic ulcers of the stomach may occur in almost any situation. When, however, the pyloric region is not involved, the ulceration is usually situated near the lesser curvature, along some point between the cardia and the pyloric portion, and all of our seventeen cases of non-pyloric ulcers were of this kind. As such ulcers spread and become more chronic, the lesser curvature itself becomes very frequently involved.

Of all lesions ulcer of the lesser curvature yields analyses which are the most obscure and the least satisfactory from a diagnostic point of view. Cases

of this condition thus fall under four of the five headings of the classification proposed in Part III. In many cases with high chloride secretion, a surgical operation demonstrated that the ulcerative process had produced an hour-glass condition of the organ. In a number of less advanced cases the chloride readings were low and even minimal, but in no case of ulcer of the body of the stomach was a condition that could be described as achylia quite attained.

The chloride and pepsin readings of cases of ulcer of the lesser curvature were on the whole distinctly lower than those of pyloric and duodenal ulcers. While, however, we regard a high chloride and pepsin reading as characteristic of the pyloric and duodenal affection, low readings are not an essential factor in the clinical picture of ulcers of other regions.

TABLE III.

17 Cases of Ulcer of the Body of the Stomach.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.	Condition of Stomach.
28	5·3	1·7	+	80	6·2	5·3	2·4	A puckered area a few inches from cardiac end extending all round stomach. Hour-glass stomach
29	6·9	4·3	+	67	8·9	7·4	2·4	Hour-glass stomach with some obstruction
30	4·4	2·4	+	50	7·0	4·6	2·6	Saddle-shaped ulcer producing hour-glass stomach with small central opening
50	4·8	1·7	+?	34	8·6	5·8	3·0	A large ulcer on posterior wall towards middle of lesser curvature
51	5·6	3·5	+	33	5·4	4·0	2·5	A large ulcer on anterior wall towards middle of lesser curvature
52	5·2	3·0	+	10	6·1	4·5	3·5	Persistent hyperchlorhydria. Ulcer in lesser curve and later of jejunum
53	6·1	4·7	+	29	9·9	7·1		Large ulcer of lesser curve ulcerating into pancreas
54	6·2	2·8	+	21	10·7	5·8		Old scar on anterior surface near cardiac end and lesser curvature
78	4·0	1·0	−	27	7·0	5·2	2·4	Large ulcer of lesser curvature
79	3·5	0·9	−?	27	5·9	4·3	2·4	Indurated ulcer extending round stomach from lesser curvature
80	4·0	0·0	−	20	5·7	4·5	4·0	Crateriform ulcer involving pancreas on posterior wall at cardiac end
81	3·9	1·9	+	19	6·6	3·2	2·5	Indurated ulcer of lesser curve close to cardiac end
82	3·8	1·9	+	19	5·2	1·9		Chronic ulcer on posterior surface near lesser curvature
83	3·3	1·7	−	19	5·8	5·5		Large gastric ulcer with much fibrosis on lesser curvature
91	2·3	0·0	−	<10	5·4	3·4		Hour-glass condition of stomach with second chamber greatly distended
92	2·2	0·0	−	<10	6·2	2·7	3·0	Depressed scar of chronic ulcer on anterior surface of stomach and lesser curvature near cardiac end
93	2·5	0·0	−	<10	7·1	3·0		Gastroptosis with old ulcer of lesser curvature

From the above table it will be seen how varied were the conditions produced by ulcer of the lesser curvature, and an explanation is thus afforded of the great variation in the analytical results. Another cause, however, of the irregularity of the analytical findings is perhaps that the stomach-tube may

bring gastric contents from either or both chambers of the stomach in hour-glass conditions. The operator has no means of ascertaining from which chamber he has withdrawn the contents.

(*d*) *On certain points in the aetiology of gastric and duodenal ulcer.* Bolton (1 and 2) has demonstrated the existence of a gastrotoxic substance which may be related to the production of a gastric ulcer, a process which is certainly aided by hyperacidity of the gastric juice. The gastrotoxic ulcer is usually in the body of the stomach. On the other hand, as we have shown in the preceding sections, the ulcers clinically associated most definitely with hyperacidity occur most frequently in the pyloric part and in the duodenum. One of us (C. S.) has found by experiments on cats that the direct action of weak acids (e. g. $\frac{N}{10}$ HCl) produces erosions more readily in the pyloric part than elsewhere. Furthermore, Edkins has demonstrated (5 and 6) that the contact of digestion products with the duodenal and pyloric mucous membrane affords the chemical stimulus to the secretion of hydrochloric acid. Lastly, it has been shown by radiographic methods (by Jordan and others (12)) in cases of duodenal and pyloric ulcer, that while the peristaltic action of the stomach may be increased and the stomach begin to empty itself sooner than in normal cases, there is yet considerable delay in and distension of the duodenum. These facts seem to us to suggest that the hyperacidity may be explained by the excitation of the chemical mechanism of the gastric secretion induced by the prolonged contact of digestion products with the duodenal mucous membrane. If the ulcer can itself be regarded as the irritative cause of increased gastric peristalsis and the subsequent duodenal stasis, we have here the elements of a vicious circle.

Such a vicious circle would explain the comparative homogeneity of analytical results obtained from uncomplicated cases of pyloric and duodenal ulcer. It also explains the regularity of the time relation of pain to the ingestion of food so characteristic a feature of these affections. In ulcer of the *body* of the stomach, however, no such circle can be produced, and thus the analytical results, as well as the clinical symptoms, are here more variable.

(*e*) *Carcinoma of the stomach.* Omitting very advanced cases and those in which there is arrest of all secretion, *sub finem vitae*, carcinomatous cases appear to fall under two chief headings according as the pylorus is obstructed or not. The most usual site for the first occurrence of the malignant process is in the pyloric canal and near the lesser curvature, while the most common mode of spread is along the lesser curvature and lesser omentum. A common site for the early formation of secondary growths is in the group of lymphatic glands which is of constant occurrence in this region. In a minority of cases, however, the growth spreads only around the pyloric orifice.[21] We thus arrive at two forms

[21] The distribution of gastric lymphatics as mapped out by Poirier and Cuneo (22) gives a clear reason for these two separate lines of lymphatic spread of gastric carcinoma. They distinguish a circum-pyloric system of lymphatic vessels from the vessels which drain a large

of carcinoma of the stomach roughly corresponding to the two types of peptic ulcer. These two forms of carcinoma, however, differ from each other not so much in the place of origin as in the direction of spread. The two forms of gastric carcinoma are morphologically parallel and produce parallel analytical results to the two forms of gastric ulcer, and we therefore distinguish between carcinoma of the pylorus and carcinoma of the lesser curvature and body of the stomach. The peptic index, however, appears to be persistently lower in carcinomatous than in ulcerous cases. This will be well seen by comparing Table IV on the one hand with Tables II and III on the other.

TABLE IV.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.	Diagnosis.
				12 Cases of Carcinoma of the Pyloric Region.				
31	6·9	4·0	+	50	10·9	6·9	3·1	Carcinoma of pylorus
32	4·3	2·5	+	50	5·8	5·2	2·8	,, ,,
33	5·0	2·1	+	40	5·8	5·0		,, ,,
57	5·7	3·0	+	29	8·5	7·1	2·3	,, ,,
55	4·9	2·2	+	22	7·0	5·2	3·4	,, ,,
56	5·6	2·6	+	10	8·0	5·0	2·5	,, ,,
84	3·5	0·7	−	31	5·8	3·3	4·4	Carcinoma of pylorus with great dilatation
85	2·8	0·6	−	26	5·6	3·5	3·3	,, ,, ,, ,,
XI[22]	2·6	0·6	−	25	5·6	1·4	3·3	,, ,, ,, ,,
XIII	2·6	0·0	−	12	5·8	2·2	3·2	,, ,, ,, ,,
86	0·8	0·0	−	11	1·6	0·6		,, ,, ,, ,,
VII	1·6	0·0	−	<10	4·6	1·7		,, ,, ,, ,,
				14 Cases of Carcinoma of the Body of the Stomach.				
94	3·9	1·8	+	<10	7·8	4·4	2·8	
97	1·5	0·0	−	<10	5·3	2·6		
98	0·9	0·0	−	<10	3·8	2·6		
95	1·8	0·0	−	<10	4·5	2·5		
112	1·4	0·0	−	<10	2·9	1·7		
96	1·2	0·0	−	<10	4·8	1·6		
116	1·5	0·0	−	<10	2·5	1·5		
114	4·6	0·0	−	<10	5·9	1·2		
118	0·8	0·0	−	<10	2·7	1·1		
117	1·0	0·0	−	<10	3·6	1·0		
115	0·7	0·0	−	<10	1·9	0·6		
V	2·1	0·0	−	<10	1·9	0·4		
111	0·9	0·0	−	<10	0·8	0·0		
113	0·0	0·0	−	<10	0·9	0·0		

Of the twelve cases of carcinoma of the pylorus that are given in the above table, all the six with no very marked obstruction show an undiminished chloride secretion, and several of these (notably Cases 31 and 57) even exhibit hyperchlorhydria. The average of the six cases gives 5·7 of secreted chloride, which is certainly above normal. It is only in the cases in which marked obstruction is present that the chloride secretion sinks below the normal

part of the body and lesser curvature of the stomach. Essentially similar conclusions have been reached on clinical and anatomical grounds by MacCarty and Blackford (16) in a recent study of the involvement of regional lymphatic glands in carcinoma of the stomach.

[22] The Roman numerals refer to cases reported in the Appendix to Part I, Vol. vi, pp. 78–81.

figure. Moreover, there is in all cases but one an appreciable peptic power, though this has not risen above normal in any single case and is in most cases unduly depressed.

A very different picture is yielded by the fourteen cases of carcinoma of other parts of the stomach enumerated in the table. In all cases except one the chloride secretion is very low. (The one exception, Case 94, in which the amount of secreted chloride reached 4·4 was a rare case of carcinoma mainly affecting the fundus.) All cases but this one show a negative Günzburg test, and with the same exception all were alkaline to dimethyl, so that uncombined hydrochloric acid was inappreciable or absent. Moreover, in no case was the peptic index above the minimal number 10.

The tables thus reveal a difference between carcinoma of the pylorus and of the body of the stomach, similar to that observed between ulcers of the same regions. We are thus led to regard the chemical differences between cases presenting lesions in the two situations as due to the site rather than to the nature of the disease. It is to be noted, however, that the rise of acidity is more closely followed by rise in peptic index in the case of ulcer than in the case of carcinoma. Thus a high peptic index becomes of great value in diagnosing chronic ulcer from carcinoma.

(*f*) *The diagnostic value of the 'nitrogen factor'*. It will have been seen from the above tables that in uncomplicated cases of duodenal and pyloric ulcer, the nitrogen factor has been consistently and uniformly low (i. e. near 2·4). This point will be found to be of diagnostic significance.

In Part III (p. 323) we have already shown that an elevation in the nitrogen factor is an accompaniment of delay in gastric evacuation. Radiographic methods, however, have recently demonstrated that in the ordinary duodenal and pyloric affection, the emptying of the stomach after ingestion of a meal takes place with abnormal vigour and rapidity (12). Thus the emptying of the stomach may commence within half an hour of the meal being taken, though the normal interval of a healthy organ is about one hour. It is therefore only in the complicated cases in which the evacuation of the stomach is impeded by stenosis of its orifice, or its peristaltic movements by disease in or adhesions of its walls, that a high nitrogen factor is likely to be encountered. We cannot yet claim to have produced adequate evidence that a high nitrogen factor is actually *diagnostic* of gastric delay, since in one or two cases in which the stomach at operation was regarded by the surgeon as normal, a high nitrogen factor was demonstrated by us. Nevertheless we have had enough experience to regard an elevation of the nitrogen factor as a strong presumption of such impediment, and its absence as greatly aiding in the exclusion of such disability.

(*g*) *Alcoholism*. Reduction of the pepsin takes place in cases of simple alcoholic gastritis. In the worse types of this condition the chlorides are lowered, but in the more typical cases the peptic power is lowered and the chloride secretion remains more or less normal. This is well brought out in the following table:

TABLE V.

8 Cases of Alcoholic Gastritis.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.
40	6·3	3·3	+	40	8·0	6·8	
61	6·7	4·4	+	30	4·9	3·6	
62	6·9	3·6	+	28	9·1	6·3	2·9
63	5·9	4·0	+	16	9·1	6·3	
64	5·6	2·8	+	10	6·8	4·6	
65	5·0	0·0	−	10	7·9	6·1	
103	3·4	0·0	−	<10	4·5	2·3	
104	2·9	0·0	−	<10	5·3	2·8	

This series of cases represents an increasing departure of analytical results from the normal in the order of descent of the peptic index and chloride.

(*h*) *On the relationship of chloride and pepsin secretion.* To what may this relative depression of the peptic index in alcoholic cases be ascribed? Chittenden and Mendel (3) have shown that alcohol has a strongly depressant influence on the digestive power of gastric juice, but in the cases that we have examined the treatment in hospital excluded the direct influence of alcohol. On the other hand, the relative depression of peptic power can hardly be due to the presence in the circulation of alcohol or its products, for the work of Metzger (18), Radzikowski (23), and Spiro (32), carried out on animals as well as on human beings, has shown that rectal injections of alcohol stimulate gastric secretion but have no specific depressant effect on the peptic power. We therefore regard the relative depression of peptic power in these cases as the result of some alteration in the mucous membrane itself. This alteration, as we have already suggested, is probably of the nature of chronic inflammatory change. To a similar cause may be attributed the wide difference between the chloride and pepsin secreting activity sometimes encountered in very chronic cases of duodenal and gastric ulcer.

We are thus led to regard the chloride and pepsin secreting functions of the stomach as to some extent independent. Such a conclusion was suggested many years ago by the work of Langley (14) and of Sewall (23), who demonstrated that pepsin could be detected in the stomachs of embryos before the secretion of hydrochloric acid had commenced. As regards the relative independence of pepsin and chloride secretions, conclusions similar to our own were reached by Schiff (26). He differs from us in the frequency with which he has encountered a relative elevation of the peptic power. The fact, however, that his estimation of pepsin was made by older methods involving the use of egg-white (Hammerschlag's and similar methods) renders this part of Schiff's work less valuable than the remainder.

In almost all the cases considered in this paper there has been a definite gastric disease, and therefore a definite alteration in the structure of the gastric wall. It is possible that the presence of toxic substances in the *circulation*

may produce a different effect to alterations in the structure of the gastric walls on the secretory activities of the stomach. That this is the case is suggested by the experimental work of Schiff himself as well as by experimental work of one of us (C. S.) now in progress, and by his conclusions in cases of chronic appendicitis (29).

(*j*) *Visceroptosis, &c.* A somewhat similar but less marked separation between peptic index and chloride secretion appears in such atonic conditions as Glénard's disease, gastroptosis, and cases with extensive gastric adhesions without other lesions. We give a series of such cases in the following table:

TABLE VI.

9 Cases of Visceroptosis.

Case Number.	Phenol Acidity.	Dimethyl Acidity.	Günzburg.	Peptic Index.	Total Chloride.	Secreted Chloride.	Nitrogen Factor.	Diagnosis.
40	4·8	2·5		40	7·0	6·0		Gastroptosis
67	5·4	0·6	–	12	7·0	5·1	3·6	,,
89	4·4	1·0	–	22	5·5	3·7	3·4	Nephroptosis
90	4·5	0·0	–	13	7·4	5·8	3·5	,,
107	2·1	0·0	–	< 10	5·4	3·7		,,
108	2·3	0·0	–	< 10	4·6	2·8		,,
109	2·4	0·5	–	< 10	6·9	2·0	3·0	,,
120	0·8	0·0	–	< 10	2·3	1·7		Visceroptosis
121	1·2	0·0	–	< 10	3·2	0·5		,,

The effects of a prolapse of the abdominal viscera on the stomach have long been recognized,[23] and the gastric symptoms associated with prolapse of the kidney have been frequently formulated. Two separate explanations of the phenomena have been given. On the one hand it has been suggested (Bartels) that the fall of the kidney by its connexion with the duodenum is liable to cause temporary obstruction of the pylorus, and on the other hand the prolapse of the kidney has been regarded (Oser) as part of a general process of visceral atony in which the stomach wall also shares.

Analytical results appear to us to give weight rather to the latter view, for if there had been merely a slight pyloric obstruction in such cases we should have been led to expect fairly high chloride secretion with increased peristaltic activity. The low amount of chloride output with the high nitrogen factor suggests, however, a condition of stasis with a general atonic condition of the gastric wall.

(*k*) *Functional hyperchylia, hypochylia, and hypopepsia.* Cases falling under these headings form the most puzzling of our collection. In those which we have given in the tables in Part III, operation was undertaken under the impression that carcinoma or ulcer was present, diagnoses fortified by the results of chemical analysis. The cases in which both chlorides and pepsin are high (hyperchylia) appear to be due to a disturbance of the secreting functions of the

[23] See Landau on 'Movable Kidney in Women' (13).

stomach, and we are unable to follow Moynihan (20) in regarding such cases as invariably the subjects of duodenal or pyloric ulcer, though our conclusions seem to show that prolonged hyperchlorhydria gives a strong presumption of the existence of one of these lesions. We would especially call attention to Case 52 (see appendix at end), in which, in spite of prolonged treatment with alkalis, gastroenterostomy and excision of ulcer, hyperchlorhydric conditions persisted and a jejunal ulcer ultimately developed.

The cases in which the chloride secretion is high and the pepsin secretion low are perhaps primarily cases of simple gastritis, as is suggested by the findings in alcoholic cases. We have in addition encountered several cases of hyperchlorhydria with a high peptic index in subjects of chronic appendicitis (see Part II, Cases 34, 35, and 36).

Finally, we have met with a few cases of functional hypochylia. We would especially draw attention to Case 125, a man of middle age with a dilated stomach. The gastric juice showed a complete absence of secretion. Nothing was found on operation except a somewhat dilated stomach. He died shortly after of pneumonia, but the post-mortem examination revealed no definite lesion but a large thin-walled stomach with atrophic mucous membrane. There was no sign of cancer or ulcer. We have already reported several such cases in Part I.

Conclusions to Part II.

1. All methods of estimating the chloride-secreting activity of the stomach by examination of gastric juice contain sources of error beyond experimental limits.

2. A proportion of 'secreted chloride' is always in combination with the amino-acid groupings of the digestion products in the form of hydrochlorides.

3. For any given amino-acid or mixture of amino-acids or digestion products (peptones, &c.) the difference between acidity to phenolphthalein and acidity to dimethylaminoazobenzene bears a constant ratio to the amount of nitrogen present. If B represents the number of c.c. of $\frac{N}{10}$ NaOH needed to neutralize 10 c.c. of a solution (e.g. a filtered gastric juice, solution of amino-acids, peptones, &c.) to phenolphthalein, and C the number of c.c. needed to neutralize to dimethyl, and A represents the number of c.c. of $\frac{N}{10}$ H_2SO_4 needed to neutralize the ammonia formed by Kjeldahlizing 10 c.c. of the solution, then for any such given solution $\frac{C-B}{A}$ is a constant. This constant multiplied by 10 we have designated the 'nitrogen factor'.

4. In healthy gastric juice the 'nitrogen factor' tends to approximate to the figure 2·4. It rarely falls below this figure, but with diminution of the digestive power and certain gastric disturbances it may rise greatly above.

5. This 'nitrogen factor' of healthy gastric juice (2·4) is higher than that of gluten fully digested by pepsin, but it is practically the same as that of a standard test-meal of tea and toast digested for an hour with a solution of pepsin of the same strength as that of normal gastric juice (50 units).

6. These results indicate that hydrochloric acid is secreted as such, and not in the form of any more complex precursor. The results also indicate the importance of nitrogen estimation for correctly interpreting titration values of gastric juice.

Conclusions to Part III.

1. Hydrochloric acid as it is secreted enters, either partly or wholly, into combination with the products of digestion. The amount thus combined depends upon the amount and character (e.g. degrees of digestion) of these products. An index as to the amount and character of these products is furnished by the nitrogen estimations and the determination of the 'nitrogen factor'.

2. 'Secreted chloride' (i.e. total chloride less inorganic chloride) is the best available index of gastric efficiency as regards hydrochloric acid.

3. The 'peptic index' and the 'nitrogen factor' are also valuable indications of gastric efficiency.

4. The amount of 'secreted chloride' and the 'peptic index' usually vary in parallel fashion. Departures from this rule are however frequent, but almost always in the direction of a relative depression of the peptic index.

5. The most satisfactory method of classifying gastric juices at present available is based on the double consideration of the amount of 'secreted chloride' and the 'peptic index'.

Conclusions to Part IV.

1. In uncomplicated cases of duodenal ulcer, the amount of 'secreted chloride' is raised together with the peptic index, while the 'nitrogen factor' approximates to 2·4. In very chronic cases the 'peptic index' is lowered and the nitrogen factor raised. In obstructed cases and cases with gastric adhesions the secreted chloride also falls.

2. The general characteristics of pyloric ulcer are similar to those of duodenal ulcer and are often even more pronounced.

3. In cases of ulcer of the body of the stomach the analytical results vary. Frequently both chloride-secreting and peptic activity are markedly depressed. In other cases the secretory activity is high. The 'peptic index' did not appear to rise above normal in any case of ulcer of the body of the stomach.

4. The characteristics of the gastric juice obtained from cases of duodenal and pyloric ulcer are capable of explanation as the result of a vicious circle, of which preternatural excitation of the pyloric and duodenal mucous membrane,

stimulation of the chemical mechanism of gastric secretion, and increased secretion are the links.

5. The analytical distinctions that prevail between ulcer of the body of the stomach and ulcer of the pylorus are also found in carcinoma of the same two regions. Hyperchlorhydria or at least euchlorhydria is common in carcinoma of the pylorus, but is not found in carcinoma of other parts of the stomach. It is therefore probable that the changes in the composition of the juice depend rather on the site than on the nature of the lesion. Carcinoma of the stomach has no specific effect on the composition of gastric juice, although both pepsin and chloride readings are generally lower than in other conditions.

6. In alcoholism the 'peptic index' is depressed while the chloride secretion remains normal or only slightly depressed. In some cases the chloride secretion is raised.

7. With visceroptosis and notably nephroptosis there is a general depression of the gastric functions. At the same time the 'nitrogen factor' is raised. The same results are associated with an atonic gastric wall.

8. Hyperchlorhydria, hypochlorhydria, and even achylia are encountered, independently of coarse gastric lesions.

9. The coincidence of a definite hyperchlorhydria with a greatly raised 'peptic index' (80 and over) is practically diagnostic of pyloric and duodenal ulcer among gastric diseases. Such cases, however, must be carefully distinguished from certain cases of chronic appendicitis in which no coarse gastric lesion is discernible. Very low chloride readings (e.g. secreted chloride below 3·0) practically exclude pyloric or duodenal ulcer.

10. A 'nitrogen factor' of 2·8 and over has been found to be almost diagnostic of delayed emptying of the stomach.

11. Dissociation of chloride and pepsin secretion is probably the result of chronic inflammatory change in the gastric mucous membrane.

REFERENCES (PARTS II, III, AND IV).

1. Bolton, C., *Proc. Roy. Soc.*, Lond., 1906, lxxvi. B. 426.
2. Bolton, C., *Proc. Roy. Soc.*, Lond., 1909–10, lxxxii. B.
3. Chittenden, R. H., and Mendel, L. B., *Amer. Journ. Medical Sciences*, Philadelphia, 1896, N. S., cxi. 35.
4. Christiansen, J., *Biochem. Zeitschrift*, Berlin, 1912, xlvi. 24.
5. Edkins, J. S., *Journ. Physiol.*, Cambridge, 1906, xxxiv. 133.
6. Edkins, J. S., and Tweedy, M., *Journ. Physiol.*, Cambridge, 1909, xxxviii. 263.
7. Ewald, C. A., *Deutsche med. Woch.*, Berlin, 1887, xiii. 1006.
8. Friedenthal, H., *Zeitsch. f. Elektrochemie*, Halle, 1904, x. 113.
9. Graham, G., *Quart. Journ. of Med.*, Oxford, 1910–11, iv. 315.
10. Günzburg, A., *Centralblatt für klin. Medizin*, Leipzig, 1887, viii. 737.
11. Herwerden, Mlle A. van, and Ringer, W. E., *Zeitsch. f. physiol. Chem.*, Strassburg, 1911, lxxv. 290.
12. Jordan, A. C., *Brit. Med. Journ.*, 1911, i. 1172.
13. Landau, L., 'Movable Kidney in Women,' *Eng. Trans.* (New Syd. Soc.), Lond., 1884.

14. Langley, J. N., *Journ. Physiol.*, Cambridge, 1880–82, iii. 269.
15. Lüttke, J., *Deutsch. med. Woch.*, Berlin, 1891, xvii. 1325.
16. MacCarty, W., and Blackford, J., *Annals of Surgery*, London, 1912, lv. 811.
17. Mathison, G. C., *Biochem. Journ.*, Liverpool, 1909, iv. 233.
18. Metzger, L., *Münch. med. Woch.*, Munich, 1900, xlvii. 1553.
19. Moore, B., *Proc. Roy. Soc.*, Lond., 1905, lxxvi. B. 138.
20. Moynihan, B. G. A., *Duodenal Ulcer*, Lond., 2nd ed., 1911.
21. Panton, P. N., and Tidy, H. L., *Quart. Journ. Med.*, Oxford, 1910–11, iv. 449.
22. Poirier, R., and Cuneo, B., *Les Lymphatiques*, Paris, 1909.
23. Radzikowski, C., *Pflüger's Arch. für die ges. Physiol.*, Bonn, 1901, lxxxiv. 513.
24. Salm, E., *Zeitsch. f. Elektrochemie*, Halle, 1904, x. 341.
25. Salm, E., and Friedenthal, H., *Zeitsch. f. Elektrochemie*, Halle, 1907, xiii. 125.
26. Schiff, A., *Boas' Archiv für Verdauungs-Krankheiten*, Berlin, 1900, i. 107.
27. Schryver, S. B., and Singer, C., *Quart. Journ. of Med.*, Oxford, 1912, vi. 71.
28. Sewall, H., *Journ. Physiol.*, Cambridge, 1878–79, i. 321.
29. Singer, C., *Lancet*, Lond., Dec. 21, 1912.
30. Sjöqvist, J., *Zeitsch. f. physiol. Chem.*, Strassburg, 1889, xiii. 1.
31. Sörensen, S. P. L., *Compt. rend. des Trav. du Lab. de Carlsberg*, Copenhagen, 1910, viii. 1 and 396.
32. Spiro, R., *Münch. med. Woch.*, 1901, xlviii. 1871.
33. Walpole, G. S., *Biochem. Journ.*, Liverpool, 1911, v. 207.
34. Willcox, W. H., *Trans. Path. Soc.*, Lond., 1905, lvi. 250.
35. Willcox, W. H., *Quart. Journ. Med.*, Oxford, 1909, iii. 93.

APPENDIX

CONTAINING CLINICAL DESCRIPTIONS OF 125 CASES.

The numbering of the cases corresponds to that of the Tables of Analytical Results.

1. **Male**, aged 41, traveller. **Symptoms**: Attacks of epigastric pain soon after food, constipation, wind, &c., for last twelve years. Vomiting occasional. Always takes flesh better than carbohydrates. Alcohol to excess, both beer and spirits. **Laparotomy**: Duodenal ulcer, clear cut with little induration.

2. **Male**, aged 48. **Symptoms**: For seven years. Onset very gradual. Unable to work for three months previous to admission. Constant gnawing epigastric pain, worst about 2 a.m. and about two hours after food. Vomiting frequent and relieves pain. **Laparotomy**: Indurated ulcer on posterior wall of first part of duodenum.

3. **Male**, aged 55, clerk. **Symptoms**: Pain after food for years. Haematemesis and melaena on several occasions. Last attack lasting a few days with vomiting of large quantity of semi-fluid blood. **Laparotomy**: Duodenal ulcer, chronic.

4. **Male**, aged 24, schoolmaster. **Symptoms**: For eighteen months pains and flushings half an hour after food, relieved by eating. Meat food suits him better than starch foods. **Laparotomy**: Ulcer in duodenum.

5. **Male**, aged 46, grocer. **Symptoms**: Indigestion for twenty-six years. Pain usually three to four hours after food, on right side and at level of umbilicus. Pain lasts about an hour and is relieved by vomiting and warmth. Often wakes him about 2 a.m. Coffee-ground vomit on one occasion. **Laparotomy**: Ulcer found in the first part of duodenum. Chronic appendicitis.

6. **Female**, aged 22. **Symptoms**: Eight years' history of attacks of vomiting and abdominal pain. Vomiting apparently unrelated to food, but precedes pain. **Laparotomy**: Scar of duodenal ulcer on upper and anterior surface just beyond pylorus. Appendix long, indurated, peritoneal surface injected, and manifest chronic inflammation.

7. **Male**, aged 33. **Symptoms and history**: Indigestion for thirteen years, worse about two years. Melaena on several occasions. Now has sense of pain and fullness about 1½ hours after food. On one occasion some haematemesis. Much pyrosis, especially in the afternoon and at night. **Laparotomy**: Large mass found in duodenum running from end of first stage down to second stage. Mass adherent to liver.

8. **Male**, aged 67, warehouseman. **Symptoms**: Dyspeptic all his life. Attacks sufficiently severe to lay him up every six months. Pain two to four hours after smallest meal, relieved by food and sodium bicarbonate. Much wasting. Haemorrhoids. **Radiograph**: Lower border of stomach level with umbilicus. **Laparotomy**: Cicatrix of old ulcer on anterior wall of first part of duodenum.

9. **Male**, aged 57, labourer. **Symptoms**: During seven years has had about twenty attacks of pain and vomiting about two hours after food. Pain relieved by eating and by bicarbonate of soda, which he always carries with him. **Laparotomy**: An indurated condition of the first part of the duodenum with an ulcer on the anterior wall. Extensive adhesions had formed between the duodenum and the liver and other viscera. Jejunum large and its walls much thickened.

10. **Male**, aged 38. **Symptoms**: For two years occasional pain one to two hours after food, sometimes relieved by eating, but more often by vomiting. Twice in hospital for this condition. No haematemesis or melaena. Much epigastric tenderness and loss of weight. **Laparotomy**: The duodenum found greatly thickened.

11. **Male**, aged 40, goods porter. **Symptoms** for ten years, including four severe attacks and some twenty less grave. On these occasions had severe haematemesis. Deep epigastric tenderness. Pain after food. **Laparotomy**: Chronic ulcer first part of duodenum.

12. **Male**, aged 63, caretaker. **Symptoms**: Numerous attacks of dyspepsia for the last twenty years. On several occasions melaena. Pain usually one hour after food. Vomiting frequent. **Laparotomy**: Chronic ulcer of first part of duodenum.

13. **Female**, aged 26, housemaid. **Symptoms**: During three years has had six separate attacks of pain about an hour after food accompanied by vomiting, and lately there has been marked wasting. **Laparotomy**: An ulcer was found on the first part of the duodenum.

14. **Male**, aged 41. **Symptoms** for eight years. Pain in back and epigastrium two to three hours after food. Much flatulence. Occasional vomiting. Rapid wasting. **Laparotomy**: An indurated ulcer of the first part of the duodenum adherent to liver and pancreas.

15. **Male**, aged 49, lavatory attendant. **Symptoms** of indefinite digestive trouble for two to three years. Pain after food referred to scapular region. Distension. Latterly, pain without relation to food. **Radiograph**: In examination showed that bismuth meal entered pylorus within half an hour and that stomach emptied quickly. **P. M.**: Death from peritonitis. Acute perforating duodenal ulcer. Carcinoma of sigmoid present.

16. **Male**, aged 47, seamanship instructor. **Symptoms** for two years. Attacks of pain two hours after food. Of late attacks have been more frequent, so that the pain is always with him. Vomiting occasionally. Haematemesis once. **Laparotomy**: Deep ulcer 3 cm. in diameter, with partly scarred and partly undermined borders on the posterior surface of duodenum reaching to within ½ cm. of the pyloric splincter. Base of ulcer formed by pancreas. Dense fibrous adhesions round duodenum. Gastroenterostomy. **P. M.**: Death a few days after operation. Melaena in duodenum. Severe haemorrhagic fibrinous peritonitis. Fatty infiltration of pericardium and atheroma of coronaries. Kidneys contained numerous pin-head adenomata and a few cysts.

17. **Male**, aged 56. **Symptoms** for nine years. Numerous attacks of pain two to three hours after food, becoming more frequent. Latterly, food relieves pain. Rarely vomits. Very constipated. Alcoholic history. Much melaena. Test for occult blood positive. **Laparotomy**: Cicatrized ulcer on first part of duodenum.

18. **Male**, aged 52, fireman. **Symptoms**: Pale, very anaemic man who had lost much weight. Marked epigastric resistance. Frequent vomiting, especially at night. Pain usually about half an hour after food, sometimes sufficiently bad to make patient shout. About a month before examination there was a severe attack of haematemesis, and on several previous occasions there had been minor attacks. Responded well for a time to treatment with alkalis and hydrocyanic acid. **Gout**: Has had very numerous attacks of gout. Father was also

a sufferer from gout and died of that disease, aged 45. Gout started when patient was 36, in left big toe, and there have been numerous attacks since. Well-marked gouty changes in feet and hands and tophi in ears. **Laparotomy**: Large pyloric ulcer completely surrounding orifice.

Analytical Results.

	Before treatment.	After six weeks' course of bismuth and soda after each meal.
Phenol acidity	11·4	6·6
Dimethyl acidity	9·2	2·8
Günzburg	+	+
Peptic index	119	33
Peptolytic ferment	−	−
Total chloride	15·1	9·5
Active chloride	11·3	8·0
Nitrogen	9·4	11·6
Phosphates (total)	5·9	8·6
Nitrogen factor	2·4	3·3

	After three months' treatment.
Phenol acidity	5·2
Dimethyl acidity	1·2
Günzburg	+ faint
Peptic index	89
Total chloride	7·9
Active chloride	5·2
Nitrogen	15·8

19. **Male**, aged 42. **Symptoms**: For ten years subject to attacks of pain half an hour after food, relieved by vomiting, eating, and Glauber's salts. Vomiting increasing in frequency. Concealed haemorrhage present in faeces. **Laparotomy**: Large chronic ulcer close to pylorus and adherent to pancreas behind.

20. **Male**, aged 29. **Symptoms**: 4½ years' history, involving occasional attacks of colicky abdominal pain accompanied by vomiting after food and constipation. **Laparotomy**: A small chronic ulcer found on posterior wall of pyloric region.

21. **Male**, aged 27. **Symptoms**: For last year has had numerous attacks of pain about one hour after food and lasting about half an hour. Eating and warmth sometimes relieve pain. Vomiting frequent. Often has pain about 2 a.m. Was in hospital with two attacks. **Laparotomy**: An ulcer was found on the anterior surface of the pyloric part of the stomach and extending into duodenum. The ulcer was firmly adherent to the left lobe of liver in front and to pancreas behind.

22. **Male**, aged 39. **Symptoms**: Digestive trouble on and off for years. Heavy dragging sensation in stomach usually comes on about 4 p.m. and about two hours after food. Pain relieved by vomiting. No history of haematemesis or melaena. Heavy smoker. Wasting. Visible gastric peristalsis. Splashing sounds. Currant meal returned 6½ hours after ingestion. **Radiograph**: With bismuth meal showed condition suggestive of dilated stomach; six hours after the bismuth the lower border was seen 3 inches below umbilicus. The stomach was pulled over to the right and very little of the bismuth had passed into the intestine. Marked peristalsis observed, and a degree of pyloric stenosis regarded as due to adhesions.

23. **Male**, aged 51, road foreman. **Symptoms**: Pain two hours after food for two months. Rarely vomiting. **Radiograph** shows rather irregular outline of stomach with completely retained bismuth more than two hours after taking meal.

24. **Male**, aged 35, labourer. **Symptoms**: Epigastric pain half an hour after food, with vomiting, three years' duration. Numerous attacks. **Laparotomy**: Small deep depression close to pylorus along lesser curvature. Depressed area excised. **Microscopic examination**: Mucosa present throughout. In centre all coats replaced by fibrous tissue. At the border the mucosa and muscularis mucosae approach each other.

25. **Male**, aged 41, printer. **Symptoms**: For last two years had had frequent attacks of epigastric pain two hours after food, relieved by heat. Latterly, pain almost continuous. Frequent vomiting. Tender spot just below and to the right of ensiform cartilage. **Radiographic examination**: Bismuth meal given and lower border of stomach distinguished fifteen minutes later 1½ inches below umbilicus. Contractions active. Second examination two hours later showed bismuth still in stomach and small intestines. Marked contractions still present. The stomach appeared to be emptying itself in normal time. **Laparotomy**: An ulcer was found in the pyloric region affecting mainly the anterior surface of the stomach and lesser curvature. Adhesions to liver. Slight dilatation.

26. **Male**, aged 36. **Symptoms**: Long dyspeptic history. Of late much pain about 1½ hours after food, with very copious vomiting. **Radiograph**: With bismuth meal the lower border of the stomach seen to be about 3 inches below umbilicus. Contractions fairly good. No bismuth seen to pass pylorus. **Laparotomy**: Stomach dilated and hypertrophied. Old ulcer found obstructing pylorus.

27. **Female**, aged 30. **Symptoms**: Pain half an hour and again three hours after food for many years. Occasional vomiting. **Laparotomy**: Scarring over pylorus. The cicatricial tissue was hard and the pylorus stenosed and not patent to finger. Stomach dilated. **Microscopic examination** showed a tiny ulcer close to pylorus.

28. **Female**, aged 46, married. **Symptoms**: Indigestion for eight years. Pain immediately after food and occasional vomiting. On one occasion haematemesis one pint. Melaena at times. **Laparotomy**: A puckered scarred area a few inches from cardiac end extending all round the stomach. Hour-glass stomach.

29. **Male**, aged 44. **Symptoms**: During seven years a number of attacks of epigastric pain and vomiting. Vomiting and food relieve pain. **Laparotomy**: Gastric ulcer of lesser curvature. The stomach was in hour-glass form amounting to obstruction.

30. **Female**, aged 47, married. **Symptoms**: Twenty years' history of indigestion with repeated admissions to hospital. Attacks frequent. Pain directly after food, especially solids. Vomits frequently. Much wasting. **Laparotomy**: Saddle-shaped ulcer of stomach adherent to liver. Hour-glass stomach, the opening not admitting finger. Adhesions in lesser sac.

31. **Male**, aged 66. **Symptoms** of six months' duration. Had never previously suffered with digestive trouble. Commenced with an attack of diarrhoea. After this patient began to vomit three to four hours after food. The regularity of this process increased, but little or no pain or even discomfort. Appetite remained good, but marked wasting. On examination stomach obviously dilated and much splashing. Only slight tenderness on pressure. **Laparotomy**: Carcinoma surrounding the pylorus. The organ was considerably dilated. Pylorectomy.

32. **Female**, aged 46, married. **Symptoms** for one year: Pain directly after food. Vomiting gradually becoming persistent. Loss of weight. Currant test-meal drawn off five hours after ingestion. Tumour in epigastric region. **Laparotomy**: A hard crateriform, carcinomatous growth surrounding pylorus.

33. **Male**, aged 48, turncock. **Symptoms**: Had all his life suffered with indigestion and constipation. For three months before being seen there was a certain amount of vomiting and discomfort. On admission the stomach was distended and vomiting frequent. No haematemesis. **Laparotomy**: There was a large ulcer extending from the lesser curvature close to the pyloric end. Enlarged glands in the lesser omentum which microscopically proved to be carcinoma. The stomach was distended and the growth extending in the pyloric region was obstructing the gastric outlet.

34. **Male**, aged 58, dock labourer. **Symptoms** of indigestion for fourteen years. Pain in sternal region directly after food; comes on in attacks. Pain not relieved by food and does not come on at night. Constipated. For two months has been hardly able to eat solids. **Laparotomy**: Stomach and duodenum normal. A definitely thickened club-shaped indurated appendix.

35. **Male**, aged 24. **Symptoms**: Four years' history of attacks of pain ½ to 1 hour after food. Relieved by fomentations, but not by eating. Constipation. Wasting. Tires rapidly. Epigastric tenderness. **Laparotomy**: Stomach normal. Fundus of gall-bladder adherent to duodenum. Multiple seed-calculi in duodenum. Evidence of chronic appendicitis.

36. **Male**, aged 30, labourer. **Symptoms** of pain after food for two years. Occasional vomiting. Definite tender spot in epigastrium slightly to right of middle line. Marked loss of weight. Haematemesis and melaena. History of enteric. **Laparotomy**: Stomach and duodenum healthy. Adherent appendix found.

		After a week's treatment with alkalis.
Phenol acidity	11·1	8·6
Dimethyl acidity	8·1	6·0
Günzburg	+	+
Peptic index	67	67
Peptolytic ferment	−	−
Total chloride	13·1	11·4
Active chloride	12·4	9·4
Nitrogen	11·2	10·1
Nitrogen factor	2·7	2·6

37. **Female**, aged 26, school teacher. **Symptoms** of gall-stones confirmed by operation. Symptoms had lasted on and off for three years.

38. **Male**, aged 43. **Symptoms**: During last five years these have been a number of gastric attacks lasting about six weeks. Pain very severe and makes him sweat. Indefinite relation to food. Definite jaundice.

39. **Male**, aged 27, goods porter. **Symptoms** of occasional diarrhoea for five years, with occasional melaena. Alcoholism well marked.

40. **Male**, aged 57, gardener. **Symptoms** for three months: Pain in chest one hour after food, with occasional vomiting. **Radiograph**: With bismuth meal showed nil abnormal; lower border of stomach at level of umbilicus. **Laparotomy**: Stomach normal except for slight prolapse.

41. **Male**, aged 35. **Symptoms** of gastric disturbance for six years. Shown to be secondary to pulmonary tuberculosis (sputum). Superior vena cava shown to be obstructed. Clubbing of fingers. Pain and vomiting two hours after food. **Radiograph** showed stomach of normal size and motility. No pyloric obstruction.

42. **Male**, aged 34, carman. **Symptoms** of fourteen years, comprising numerous attacks lasting about three months, with fair health between. Pain, vomiting, and loss of weight in attacks. Pain in sternal region eased by alkalis and bicarbonate of soda. Pain two to three hours after food with much vomiting. **Laparotomy**: Nil abnormal found in stomach or elsewhere.

43. **Male**, aged 55, joiner. **Symptoms**: Long history of indigestion. Heartburn two hours after food, especially after pastry and farinaceous substances. Always relieved by alkalis. **Laparotomy**: Stomach, duodenum, and gall-bladder normal.

44. **Female**, aged 46, tailoress. **Symptoms** of indigestion all adult life. Pain directly after food and lasts two to three hours, relieved by alkalis. Epigastric tenderness. **Laparotomy**: Submucous uterine fibroid removed. Stomach and duodenum normal.

45. **Male**, aged 44, teacher. **Symptoms** of indefinite onset, following typhoid. Mitral incompetence. Hunger pain one hour after food, occasional vomiting. Stomach in inflation extends two inches below umbilicus.

46. **Male**, aged 49, clerk. **Symptoms**: Eight years previously had a sudden attack of abdominal pain. He was taken to hospital and found to have a perforated duodenal ulcer, for which he was operated upon. The ulcer was sewn up. He remained quite well for 6½ years. During eighteen months before readmission had had about eight attacks of severe abdominal pain. Hunger pain well marked. Frequent vomiting, which relieved pain. **Laparotomy**: Stomach and omentum very adherent to old scar. Ulcer present on posterior wall of duodenum just below pylorus.

47. **Male**, aged 44, commercial traveller. **Symptoms**: Attacks of pain and vomiting for five years. Pain in right hypochondrium without relation to food, but often at 2 a.m. **Laparotomy**: Numerous adhesions in pyloric region. Small scar found on anterior aspect of first

part of duodenum and a large scar involving the pancreas on the second part. Gastric adhesions. **Microscopic examination** of portion of mucous membrane removed from cardiac end of stomach showed neither mucous catarrh nor polymorph infiltration of the membrane itself on interstitial tissues. A few well-developed lymphoid nodules.

48. **Male,** aged 40. **Symptoms** for three years: Pain one to two hours after food, and latterly vomiting. Attacks last only a few days. Loss of weight. Pain very localized, sharp, and relieved by alkalis or food. **Laparotomy:** Large, very hard chronic ulcer occupying the whole of the anterior wall of first part of duodenum.

49. **Male,** aged 49, station-master. **Symptoms:** Six months' history. Gradual wasting, indefinite dyspeptic symptoms. Pain not a marked feature, usually one hour after food. **Laparotomy:** Extensive growth observed, mainly in transverse mesocolon. **Post-mortem:** A mass of lobulated growth in fundal region of stomach. An ulcer with carcinomatous infiltration on posterior surface of greater curvature. Secondary nodules on peritoneum and in liver. Chronic gastric ulcer on lesser curvature and acute duodenal ulcer 3 cm. from pylorus. **Microscopically** medullary carcinoma.

50. **Male,** aged 50. **Symptoms:** For two years had been subject to attacks of vague abdominal pains becoming gradually more definite and developing into pain about two hours after food. At a laparotomy a year before admission only a few peritoneal adhesions were found. The stomach was opened at the time and found to be normal. **Laparotomy:** A large ulcer found on posterior wall towards the middle of the lesser curvature.

51. **Male,** aged 38, cabinet-maker. **Symptoms:** Epigastric pain half an hour after food for nine months. Unable to work for six weeks and pain becoming constant instead of related to food. Stomach much distended to left. **Laparotomy:** Large chronic ulcer on anterior surface and lesser curvature in middle of stomach producing hour-glass effect.

52. **Male,** aged 29, gas-meter maker. **Symptoms and history:** First attack ten years previously, lasting three months. Pain in right hypochondrium after food ½ to 4 hours. Frequent vomiting at height of attack. Patient came under observation 11/11/11 in fifth attack. 21/11/11 **Laparotomy:** Small ulcer on lesser curvature. Ulcer excised and posterior gastrojejunostomy performed. After operation patient improved for a short time, but then began to relapse. Vomiting again frequent and was not relieved by bismuth and soda (note high peptic index had set in). He was again admitted and a second analysis made immediately after admission, and a third after a few days, dieting and treatment with bismuth and soda. A second operation 13/2/12. Scar of old ulcer sound, but the anastomosis acting badly and a large inflammatory mass around its margin. An ulcer was present on the gastric side of the stitch line and a large jejunal ulcer immediately beyond the stomach. The ulcer and the limbs of the anastomosis removed. An analysis was made before he left. In a few weeks, however, the symptoms returned yet again.

	17/11/11		21/11/11	7/2/12	12/2/12	13/2/12	28/2/12	3/3/12
Phenol acidity	5·2	Gastroentero-stomy.	6·4	Dieted. Treated with bismuth and soda.	5·8	Excision of anastomosis.	6·4	6·3
Dimethyl acidity	3·0		4·3		2·9		3·3	3·0
Günzburg	+		+		+		+	+
Peptic index	10		67		31		22	25
Peptolytic ferment	–		+		–		–	–
Total chloride	6·1		10·4		6·9		8·1	8·3
Secreted chloride	4·5		7·4		6·2		6·9	6·8
Nitrogen	6·3		9·6		10·9		14·0	12·1

Diagnosis: Hypopepsia. Persistent hyperchlorhydria. Ulcer on lesser curve and later in jejunum.

53. **Male,** aged 65. **Symptoms:** Gradual onset for thirteen months of pain about one hour after food, finally lasting all day and made worse by eating. Vomiting very rare and never copious. **Laparotomy:** Enlarged tail of pancreas the size of a tennis ball. Large ulcer extending from lesser curvature had ulcerated into pancreas.

54. **Female,** aged 36. **Symptoms** for eight months: Epigastric pain immediately after, later ½ to 2 hours after food. Sometimes sinking feeling, relieved by food and by lying down. Pain at times very severe. Haematemesis on several occasions. Movable right kidney. Gastric dilatation. **Laparotomy:** Stomach and duodenum normal, but old scar on anterior surface near cardiac end and close to lesser curvature.

55. **Male,** aged 66, house decorator. **Symptoms** commenced insidiously three years before admission. At first indefinite feeling of depression and occasional vomiting. Later epigastric and interscapular pain after food, relieved by vomiting and by taking bland fluids such as milk. **Laparotomy:** Carcinomatous ulcer in pyloric region, secondary deposits in liver. Inoperable.

56. **Male,** aged 45. **Symptoms:** Gradual onset for two months only. Began with dyspeptic attacks lasting one or two days. These became more frequent and passed into general abdominal pain and later vomiting after food. Much loss of weight. No previous history of indigestion. **Laparotomy:** Large carcinomatous mass involving pylorus with small secondary nodules on under-surface of liver. Stomach hypertrophied. Pyloric obstruction.

57. **Male,** aged 68, japanner. **Symptoms** of indefinite dyspepsia for two months. Blood in faeces. **Laparotomy:** Primary carcinoma of sigmoid. Numerous nodules in lesser omentum involving pylorus and causing some obstruction.

58. **Male,** aged 41, butcher. **Symptoms** of gall-stones for two years. **Laparotomy:** Multiple small black stones found in bladder. One stone in cystic duct.

59. **Female,** aged 62. **Symptoms** for six months: Marked loss of weight. Pain after food, relieved by vomiting. Occasional icterus. Enlarged gall-bladder. **Laparotomy:** Gall-stones.

60. **Male,** aged 53, newsagent. **Symptoms** of gall-stones of seven years' duration confirmed by **operation.**

61. **Male,** aged 35, labourer. **Symptoms:** Morning sickness, jaundice, and vomiting directly after food for ten weeks. Very heavy drinker, practically lives on beer. Tubercle bacilli in sputum—both apices in early stage of tuberculosis.

62. **Female,** aged 21. **Symptoms:** Epigastric and right hypochondriac pain immediately after food. Haematemesis. Prolapsed right kidney. Vomiting always first thing in morning. Alcoholic history.

63. **Male,** aged 49, labourer. **Symptoms** for four years: Pain in chest on and off ½ to 2 hours after food, relieved sometimes by vomiting or food. Haematemesis on two occasions. Much wasting. Stomach dilated. Strong alcoholic history.

64. **Male,** aged 61, cabinet-maker. **Symptoms** for many years: Pain 1½ hours after food. In hospital on two occasions with diagnosis of 'gastritis'. Alcoholic.

65. **Female,** aged 46, married. **Symptoms** of indefinite gastric character for six years. Of late nausea with morning sickness. Constipation. No hepatic enlargement. Fats especially disagree. Strong alcoholic history.

66. **Male,** aged 57. **Symptoms:** Obvious portal obstruction due to cirrhosis of liver of gradual onset. The veins on the abdominal walls enlarged. Ascites, haemorrhoids present. Liver and spleen large. Blood count: red cells 62,500, haemoglobin index 80 per cent., white cells 3,600. Differential count presented no points of interest. A meal of currants was given and none were found six hours afterwards.

67. **Female,** aged 37. **Symptoms.** Indigestion for many years, with pain after food and much flatus. On one occasion several years ago there was a severe haematemesis. A few weeks before admission another haematemesis with much melaena. **Laparotomy:** Stomach prolapsed, otherwise normal.

68. **Female,** aged 53. **Symptoms** of indefinite dyspeptic pain for eight years. Right kidney felt distinctly movable. Pain usually lasted about an hour and came on about an hour after food. Constipation. Pain relieved by vomiting. **Laparotomy:** Right kidney found very mobile. Nephropexy.

69. **Male,** aged 41. **Symptoms:** Pain referred to abdomen or colicky character one to two hours after food. Much diarrhoea accompanied by slime, suggestive of mucous colitis.

Diarrhoea alternates with constipation. Much wasting. **Laparotomy**: Nothing abnormal in stomach, duodenum, or colon.

70. **Female,** aged 28. **Symptoms**: Several attacks of abdominal pain about half an hour after food. During three days before admission had eight attacks of haematemesis. Red cells 2,900,000, haemoglobin 35 per cent., colour index 0·66. **Laparotomy**: Stomach opened. Stomach and duodenum apparently normal. Culture taken—nil abnormal. Appendix removed (? normal).

71. **Female,** aged 24. **Symptoms**: Pain in epigastric region ten minutes after food, lasting about half an hour, on and off for a year. Vomiting about every other day. Haematemesis. **Laparotomy**: Gastric mucous membrane carefully examined, but no lesion found.

72. **Female,** aged 56. **Symptoms.** Pain soon after food for some weeks. After few hours vomiting takes place, the vomitus being only clear fluid. Stomach not dilated. Constipated.

73. **Male,** aged 35. **Symptoms**: Knife-like anginal praecordial pain on making muscular effort. Relieved by rest and purges. Has been in hospital several times for this affection, which has lasted some months. High blood pressure and arteriosclerosis.

	Analytical Results.	Four days later.
Phenol acidity	7·1	7·1
Dimethyl acidity	4·1	4·1
Günzburg	+	+
Peptic index	17	17
Total chloride	8·9	8·5
Active chloride	5·9	5·3

Diagnosis: Hypopepsia, hyperchlorhydria, pseudangina.

74. **Male,** aged 54. **Symptoms** for the last few weeks of faintness, melaena, and haematemesis. Has had similar attacks.

75. **Male,** aged 32, carpenter. **Symptoms** for two years: Pain 1½ hours after food, especially at night, and relieved by eating. Frequent copious vomiting. Attacks last about a week and are relieved by dieting. Small tender spot in middle line one inch above umbilicus. **Laparotomy**: Ulcer in first part of duodenum just past pylorus and chiefly on lower and posterior aspect. Some gastric dilatation.

76. **Male,** aged 55, decorator. **Symptoms**: Digestive trouble for years. Attack of pain lasting three to four days in epigastrium, relieved by food, vomiting, and hot poultices. Vomiting from time to time for five years with occasional haematemesis. Of late, vomiting daily of several pints. **Laparotomy**: Extremely chronic scar of first part of duodenum. Stomach much dilated and atonic.

77. **Female,** aged 43. **Symptoms** for twenty years: Numerous attacks of pain, anorexia, and vomiting lasting two to four weeks. Perfectly well between attacks. Much wasting. Pain chiefly in back ½ to 3 hours after food, relieved by vomiting but not by eating. Visible peristalsis. On one occasion coffee-ground vomit. Red corpuscles 1,750,000, haemoglobin index 10 per cent. **Laparotomy**: Hard mass of ulcerous origin in first part of duodenum, with extensive gastric adhesions. Marked pyloric obstruction and extreme gastric dilatation.

78. **Male,** aged 63, French polisher. **Symptoms**: Pain in chest and epigastrium 1½ to 2 hours after food, relieved by eating. During the last three years he has been distinctly worse, and for some months pain has been almost continuous and he has been unable to work. A year previously was in hospital for haematemesis. Wasting marked. **Laparotomy**: Large ulcer of lesser curvature.

79. **Female,** aged 29, married. **Symptoms** for many years, much worse for last two months: Pain one hour after food. Vomiting occasionally. Haematemesis. Rapid loss of weight. **Radiograph** shows hour-glass stomach. **Laparotomy**: Thick indurated ulcer extending round stomach from lesser curve in cardiac region and giving rise to an hour-glass effect.

80. **Female,** aged 46. **Symptoms**: Indigestion for twenty years, worse for last seven. Numerous attacks lasting three to five months. Pain one to two hours after food, relieved by lying on back, but no relief by eating or vomiting. Unable to eat meat for years.

Laparotomy: Ulcer on posterior wall of stomach at cardiac end. Ulcer crateriform and involved pancreas.

81. **Male,** aged 38. **Symptoms**: Indigestion for 3½ years. There were attacks of pain in chest one hour after food. One severe haematemesis, but seldom vomited. Last attack very severe and lasted six weeks. Much loss of weight. **Laparotomy**: Indurated gastric ulcer on lesser curve too high up for excision. Gastroenterostomy. Haematemesis after operation.

82. **Male,** aged 35, fireman. **Symptoms** for two years: Began as simple flushing of nose and malar area after full meals, especially with meat. After six months pain set in with tenderness over a very definite area in left hypochondrium. Pain after every meal, but was relieved by belching or lying down. Latterly he had been vomiting chiefly in the early hours of the morning. **Laparotomy**: A large chronic ulcer on posterior surface of stomach near lesser curve.

83. **Male,** aged 42. **Symptoms** of twelve years' duration, during which there had been about ten attacks lasting three weeks. Was in hospital through several attacks. Haematemesis mostly at 4 p.m. Vomiting frequent, usually in afternoon. Pain very soon after food and relieved by alkalis. **Laparotomy**: Large gastric ulcer found in lesser curvature. Excision and gastroenterostomy. **Microscopically** a simple ulcer with much fibrosis.

84. **Male,** aged 46. **Symptoms** of epigastric pain one hour after food and wasting for one year. Pain waked him at 1 a.m. Visible peristalsis and dilated stomach. **Laparotomy**: Inoperable carcinoma of pylorus with metastases in mesentery.

85. **Male,** aged 61. **Symptoms**: Vomiting large quantities for ten weeks, improved with lavage. Wasting. Thirst. Visible abdominal peristalsis. Five pints drawn off from stomach. Tumour felt. **P.M.**: Stomach greatly dilated. Greater curvature reached pubes. A hard annular carcinomatous mass occupied the pylorus. Metastases in mesentery, in fundus, and elsewhere.

86. **Male,** aged 51, clerk. **Symptoms**: Rather sudden onset four months previous to admission. Epigastric pain without definite relation to food. Vomiting one to four times daily, on one occasion 'coffee grounds'. **Laparotomy**: Large, hard carcinomatous mass on posterior wall of stomach in pyloric region. Pancreas deeply involved. Inoperable.

87. **Male,** aged 33, clerk. **Symptoms**: Many attacks of indigestion during last two years. Pain of short duration and not related to food. No vomiting. Occasionally jaundiced with white stools. **Laparotomy**: Gall-stones and cholecystitis. Adhesions of gall-bladder to stomach. Hartmann's pouch much distended.

88. **Female,** aged 45, married. **Symptoms**: Five weeks' jaundice, vomiting, and wasting. Liver small. Bile and trace of sugar in urine. Alcoholic. Commencing ascites. **Diagnosis**: Cirrhosis of liver.

89. **Female,** aged 37, married. **Symptoms** since confinement four months before admission, consisting of pain in back and lower abdomen, palpitation, &c. Frequent vomiting since birth of last child. Mobile kidney. **Operation**: Nephropexy.

90. **Female,** aged 39, married. **Symptoms**: Dyspepsia for twenty years with occasional vomiting. Vomits more frequently of late. Losing flesh. Constipation. Well-marked mobility of right kidney. **Operation**: Nephropexy performed. For description of this case see Part III.

91. **Female,** aged 42, married. **Symptoms**: Pain immediately following food with tendency to vomit half an hour after for many years. Haematemesis two years previously, followed by first **Operation**, at which a large deep ulcer was found near cardiac end and on lesser curvature. Hour-glass condition of stomach. Patient well till two months before admission, when vomiting and pain after food set in and another haematemesis. Second **Operation** showed that second chamber of stomach was distended.

92. **Female,** aged 56, married. **Symptoms**: Ten years' history of dyspepsia, pain two hours after food, and occasional vomiting. One month before admission symptoms became more severe and definite. A vomit almost daily relieves her. Haematemesis three separate occasions in one week. **Radiograph** shows lower border of stomach one inch below umbilicus. **Laparotomy**: Depressed scar of chronic ulcer on anterior surface of stomach and lesser curvature near cardiac end.

93. **Female,** aged 47. **Symptoms,** &c.: Pain in epigastrium from time to time for twenty-five years, chiefly one hour after food, relieved by eating and by vomiting. Of late pain

continuous and not related to food. **Laparotomy**: Gastroptosis. Old ulcer of lesser curve. Pylorus not obstructed.

94. **Female,** aged 52, married. **Symptoms**: For two months epigastric and left scapular pain half an hour after food, relieved by vomiting. Marked wasting. Subcutaneous abdominal nodules. No tumour. No enlargement of stomach. **Laparotomy**: Inoperable mass of carcinoma in fundus of stomach. Secondary growth in omentum.

95. **Male,** aged 42. **Symptoms**: Sudden onset four months before admission. Pain indefinitely related to food, but worse with solid diet. **Laparotomy**: Carcinomatous mass the size of fist on lesser curvature and anterior wall adherent to liver. Stomach not dilated. Inoperable.

96. **Male,** aged 56, clothier. **Symptoms**: Four years' history involving several attacks of slight epigastric pain, wind, &c. Pain fifteen minutes after food, relieved by vomiting. **Laparotomy**: Extensive carcinoma of lesser curvature and pyloric region. Inoperable.

97. **Male,** aged 51. **Symptoms**: Indefinite duration of about six months. Pain almost immediately after food in epigastrium and chest, extending thence all over abdomen. Vomiting frequent, but does not relieve pain. Marked wasting. **Laparotomy**: Carcinoma along posterior wall of stomach and greater curvature, with numerous minute nodules on peritoneum. Pylorus patent. Inoperable.

98. **Male,** aged 40, engineer's labourer. **Symptoms**: Four months' history. Pain always present, but gets worse about one hour after food. Vomiting occasionally. **Laparotomy**: Large inoperable carcinoma spreading along lesser curvature and infiltrating liver.

99. **Male,** aged 30, iron founder. **Symptoms**: Pains at times behind sternum, slightly but not completely eased by bicarbonate of soda. Occasional vomiting about one hour after food. Attacks of jaundice. Losing weight. Constipated. **Radiograph**: With bismuth meal showed a small stomach, the lower border of which was an inch above umbilicus. The stomach appeared to empty itself abnormally quickly. **Laparotomy**: Numerous adhesions of stomach to surrounding viscera.

100. **Female,** aged 43, married. **Symptoms**: For twelve months before admission suffered with attacks of epigastric pain lasting a few days and making her keep her bed. The pain was not definitely related to food, but associated with vomiting chiefly in the early morning. Marked loss of weight. **Laparotomy**: Stomach found greatly dilated with numerous perigastric adhesions. Stomach opened, but no growth or ulcer was found. The patient subsequently responded well to medical treatment and left hospital free from symptoms.

101. **Female,** aged 52. **Symptoms**: Typical history of gall-stones for some years. Operation three years before admission and biliary fistula ever since. Of late a great deal of vomiting and constant feeling of nausea. **Operation**: Fistula excised. Stomach extensively adherent.

102. **Female,** aged 47. **Symptoms**: Attacks of pain in the mid epigastric region very severe and causes patient to sweat and vomit. During attacks vomits five or six times a day. Gall-bladder felt distended. **Laparotomy**: Big gall-bladder full of stones. Dilated common duct full of stones. Gastric adhesions.

103. **Male,** aged 32, dock labourer. **Symptoms**: Pain indefinite time after food for five months. Alcoholism.

104. **Female,** aged 28. **Symptoms**: Had always been subject to attacks of 'gastritis', and several times in hospital with this condition. Always diarrhoea during attacks, with cramps in legs and pins and needles. Alcoholic neuritis.

105. **Female,** aged 29, machinist. **Symptoms**: For two years the signs and symptoms of an atrophic cirrhosis of the liver had been becoming more obvious. There was well-marked ascites with oedema of legs and lumbar region.

106. **Female,** aged 50, married. **Symptoms**: Weakness and wasting. Pain and occasional vomiting immediately after food, two years' duration. Severe haematemesis on two occasions. **P.M.**: Hobnail liver. Enlarged spleen. Varicosity of oesophageal veins.

107. **Male,** aged 24, machinist. **Symptoms**: Complained of epigastric swelling and pain half an hour after food. No vomiting. Well-marked gastric dilatation. Tachycardia and cardiac hypertrophy. Did well when taken off tobacco, dieted, and treated with bismuth and soda. Movable kidney.

108. **Female**, aged 46, married. **Symptoms**: Indefinite. Pain in loins for years, better during pregnancy. No relation to food. **Radiograph** shows lower border of stomach 2 inches below umbilicus. Stomach contracts well. **Laparotomy**: Gastroptosis with mobility of right kidney.

109. **Female**, aged 46. **Symptoms**: Pain directly after food for about a year. Occasional vomiting. Much wasting. **Operation**: A slightly dilated pelvis of the kidney.

110. **Male**, aged 67, farmer. **Symptoms**: For four months had been constipated and had gnawing pain especially after food, and worse at night. Teeth very defective. Flatulence and occasional vomiting. **Laparotomy** showed stomach, duodenum, and gall-bladder normal.

111. **Female**, aged 40, married. **Symptoms** of indigestion, heartburn, water-brash, and pain between the shoulders for years. A year before admission these attacks returned with increasing severity and vomiting. **Laparotomy**: Enormous carcinoma extending along lesser curvature into pancreas. Extensive ulceration in several parts of gastric mucous membrane.

112. **Male**, aged 49, labourer. **Symptoms**: For five months pain in stomach dull or sharp in character, but always present and without relation to food. Vomiting frequent; occasional haematemesis. Large tumour in epigastric region, glands in neck, evidence of metastases in thorax. Enlarged glands in left axilla. Wasting marked.

113. **Female**, aged 47, married. **Symptoms** for last two years, and much worse for last two months. Much pain, setting in soon after meals. Much vomiting; the vomitus usually contains a large amount of mucus. Visible peristalsis and tumour. **Laparotomy**: A diffuse colloid carcinoma of stomach extending from lesser curvature and involving most of stomach wall. Inoperable. Patient died a few weeks later.

114. **Male**, aged 60, greengrocer. **Symptoms**: Five months' history. Commenced with attack of pain half an hour after food, which lasted longer and longer till on admission the pain was continuous. **Laparotomy**: Inoperable carcinoma of stomach. A very extensive infiltrating growth. The greater part of the mucous membrane of the stomach had sloughed.

115. **Male**, aged 51, bandmaster. **Symptoms**: Heartburn and water-brash on and off all his life, usually relieved by alkalis. In the last few months this has been getting worse and no relief can be obtained except by vomiting. Rapid loss of weight. **Laparotomy**: Large inoperable carcinoma extensively involving stomach, especially in region of lesser curvature.

116. **Female**, aged 53, married. **Symptoms** for three months before admission. Pain a variable time after food has been a constant factor, but little or no vomiting. **Laparotomy**: Extensive nodular growth involving a great part of the stomach wall. **P.M.** showed growth infiltrating the whole of the stomach.

117. **Male**, aged 68. **Symptoms**: Pain and vomiting half an hour after food for two years. **P.M.**: A malignant ulcer with ragged surface in cardia, 7 inches long, with central perforation.

118. **Male**, aged 54, engineer. **Symptoms**: Indefinite history of two years' duration. Epigastric pain, increasing two to three hours after meals, and not relieved by vomiting. Haematemesis on one occasion. Marked wasting. No tumour felt. **Laparotomy**: Masses of carcinomatous growth all round cardiac end, with nodules above the lesser curvature. Inoperable.

119. **Female**, aged 36, married. **Symptoms and history**: One month ago took salts of tartar. Very ill at time and almost constant vomiting since. **Laparotomy**: Stomach distended and walls greatly thickened. Pylorus almost completely blocked.

120. **Female**, aged 49, married. **Symptoms**: Indefinite and long history of abdominal pain and occasional vomiting. Wasting. Pain without relation to food. Occasional haematemesis. Abdomen lax, twelve pregnancies. **Laparotomy**: Several visceroptoses. Edge of liver reaches down to well below false brim of pelvis. Both kidneys freely movable. Stomach prolapsed but otherwise normal. Long gastro-hepatic omentum.

121. **Female**, aged 43, married. **Symptoms**: Appendix removed four years previously, since then dyspeptic pain soon after food, worse for three months. Vomiting occasional. **Laparotomy**: Stomach and duodenum explored, but no abnormal condition found.

122. **Female**, aged 46. **Symptoms** for four years: Short of breath, oedema of legs, jaundice. Enlarged liver. Alcoholism.

123. **Male**, aged 36, carman. **Symptoms**: Occasional attacks of griping pain ½ to 1 hour after food. These attacks had been getting worse, and latterly accompanied by vomiting. Very constipated. Responded to medical treatment.

Analytical Results.

	31/1/12	12/2/12	11/3/12
Phenol acidity	2·0	8·0	5·1
Dimethyl acidity	< 0·0	0·0	3·6
Günzberg	−	−	+
Peptic index	10		
Peptolytic ferment	−		
Total chloride	3·1		
Active chloride	0·0		
Nitrogen	4·9		

124. **Female**, aged 43, married. **Symptoms**: For years has suffered with dyspeptic symptoms. Meat and flesh always gave her great pain. Difficulty in swallowing due to spasmodic stricture of the oesophagus—organic stricture excluded by observation of bismuth meal and by a passage of bougie. **Diagnosis**: Achylia.

125. **Male**, aged 46, carpenter. **Symptoms**: For years has suffered with indigestion. Pain comes on at an irregular time after food and may be very severe. For last year has been much worse and constantly belching. **Laparotomy**: Nil found. **Post-mortem**: A large atonic stomach. No organic disease. **Diagnosis**: Achylia, gastric atrophy

THE QUANTITATIVE ESTIMATION OF AMYLOLYTIC FERMENTS IN THE URINE AS A MEASURE OF CERTAIN PATHOLOGICAL CONDITIONS[1]

By DUDLEY CORBETT

Until recent years the subject of this inquiry has received little attention, although Cohnheim in 1863 (6) showed that human urine contained a ferment which was capable of reducing starch. Such literature as there is has almost entirely been contributed by Continental workers; only two papers have been found in English dealing therewith. Recent text-books on physiology dismiss it in a few words. Michael Foster (9), in 1867 referring to the work of Cohnheim, confirms the presence of this ferment and discusses the question as to whether it is of the nature of a protein. He states that if it is not a protein one should be able to dissociate it from protein and obtain a fluid possessing strong amylolytic powers and yet not giving the protein reactions. This he showed to be possible: 'If urine is mixed with three or four times its bulk of alcohol, the deposit filtered off, washed with alcohol, extracted with cold water and filtered, the filtrate forms an amylolytic fluid often giving no visible proteic reaction.' He states further: (1) The time for the conversion of a given quantity of starch is proportional to the amount of ferment present. (2) The greater the dilution of the starch, the more rapidly does a given amount of ferment work. (3) The presence of neutral salts, chlorides and sulphates of Na, K, &c., even to saturation has no appreciable effect. (4) The effect of the addition of acids and alkalis depends upon the degree of their concentration. As concentration increases so there is first delay, then action is suspended, though it will return again after neutralization, and finally the ferment is completely destroyed. (5) The ferment action is catalytic.

The following facts, he says, seem to indicate that the urine is merely a channel for the excretion of a certain amount of ferment contained in the blood. The amount of ferment in urine is increased after meals; i. e. one hour's urine passed after food acts more rapidly on a given quantity of starch than one hour's urine passed when the stomach is empty. In man both blood and urine are amylolytic, and so are those of the pig and rabbit. On the other hand,

[1] A thesis presented for the degree of D.M. in the University of Oxford.

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sheep's urine has a feeble action, and that of its blood is almost nothing. He found that in man the amount of ferment in the urine was the same whether on an animal or vegetable diet. It had been suggested that diabetes was due to an excess of ferment in the blood, but he was unable to find that either the blood or the urine contained more diastase than in health.

Many years later Clark (5) showed the presence in urine of a substance which changed starch into sugar. It did not work in an alkaline medium, and was unaffected by the addition of thymol. Boiled urine had no reducing action on starch. He added to urine five times its bulk of absolute alcohol, and obtained a precipitate which when dried was a white amorphous powder containing chlorides, sulphates, and phosphates, and a substance which acted on starch. A solution of this powder was found to be less active than the urine itself. A glycerin extract was then made by evaporating urine to a small bulk at a low temperature and pouring glycerin over the semi-solid residue. This glycerin extract was very active, more active than the powder or even the urine itself. He does not, however, state whether this extract was made up to a volume corresponding with the urine taken. He found that the amylolytic substance acted best in an almost neutral medium, and that the presence of chlorides, phosphates, and sulphates had no effect upon its activity. In diabetic urine he was unable to find any of the ferment, and while suggesting that diabetes might accordingly be due to the retention of the ferment in the blood, he brings forward no experiments in support of this hypothesis.

It is after all only to be expected that the soluble constituents of the digestive secretions should be absorbed by the blood. In this connexion Rohman (15), Bial (2), Wohlgemuth (22), and others have found diastase in the blood. Hanriot (10) has found a lipase in the serum which decomposes butyrin and neutral fats. Although it is generally admitted that butyrinase exists, the property of this lipase to split olein and other neutral fats is disputed. Hedin (11) has confirmed and further studied the presence of a weak proteolytic ferment first described by Delezenne and Pozerski (8). An anti-enzyme has been found for this as well as for other ferments, such as rennin and trypsin. Some other ferments reappear in the urine. Wilenko (21) has examined quantitatively the presence of a pepsin, and Braunschweig (3), and later Rosenthal (18), have shown that this ferment, present in health, is absent in cases of diabetes insipidus. Opie (13) found a fat-splitting ferment in a specimen of urine taken after death from a case of acute pancreatitis; on the other hand, Robson and Cammidge (16) have been unable to demonstrate the presence of such a ferment in cases of subacute and chronic pancreatitis.

As regards the amylolytic ferment little progress was made until Wohlgemuth (23) in 1908 devised a method of quantitative estimation, which he further elaborated in 1910 (24) and 1911 (25). A large amount of his work was carried out with specimens of urine obtained by double ureteric catheterization from cases where it was probable that one kidney was damaged by disease. By estimating the amount of ferment present in either specimen he is able to say

which of the two kidneys is affected, for the diseased kidney will excrete less diastase than the normal one. This method he considers simpler and of greater value than the indigo carmine, phloridzin, or freezing-point tests. The hypothesis that less diastase would probably be excreted by a damaged kidney he was further able to confirm by examining a series of urines from cases of nephritis. The quantity of ferment was always less than that found in the normal. The work of Wynhausen (26), v. Benczur (1), and Rosenthal (18) is in agreement with these results. They all find that in the greater number of cases of nephritis, especially in the chronic interstitial form, the amount of diastase in the urine has considerably diminished.

Further, Hirata (12) has shown that if the kidneys of the rabbit are artificially injured, diastase diminishes in the urine in proportion to the progress or extent of the disease thus induced.

Wohlgemuth therefore takes this variation in the excretion of diastase as a means of estimating the functional activity of the kidneys. It will be shown later, however, that this is only a limited application of the test. The results obtained when investigating various pathological conditions are dependent on other factors besides renal efficiency, and so are only reliable within certain limits. A complete absence of diastase does not mean complete cessation of functional activity, nor, on the other hand, does a very large rise in the output of ferment mean a corresponding increase in function, but rather an indication of the amount of diastase in the blood.

Technique.

As the technique of the work here recorded has exactly followed that devised by Wohlgemuth, it will be given in detail. The only difference is that for the purposes of this research a portion of a twenty-four hours' specimen was taken from any given case wherever possible.

About 3 c.c. of urine are sufficient for carrying out the estimation. It need not be examined at once, for by the addition of toluol in the proportion of 1 to 10 it can be used for the test after some weeks, if shaken up occasionally. Indeed, there is very little deterioration even after six months. Unless the urine contains any gross impurities it need not be filtered before use. The salt content is without any influence on the result, nor is it necessary to pay any attention to the reaction. When dealing with urines obtained by catheterization from either kidney, where a differential diagnosis of functional activity is required, the estimation of the lowering of the freezing-point can be carried out without there being any risk of damaging the contained ferment. Similarly, the indigo carmine and phloridzin tests can be carried out on the same samples, for neither of these substances has any effect on the diastase estimation. In this connexion, however, one should be careful that urine for the test has been collected at the same time from the right and left kidneys; for a great difference

may arise if urine from one kidney is used which has been excreted earlier or later than that collected from the other.

Wohlgemuth (25) gives the details of two tests, one where the urine is digested with starch for twenty-four hours, and the other for half an hour. He states that the differences are better marked in the twenty-four hours' test, but for general purposes the half-hour test is sufficient. Further, the half-hour test has been used by the majority of other observers, and so the figures obtained are comparable. It has therefore been used here.

Solutions required. (1) 2–3 c.c. urine.

(2) 0·1 per cent. solution of 'soluble starch' (Kahlbaum, Berlin) in distilled water. This is best prepared by having the water boiling in an open beaker on a sand-bath and gradually adding the requisite amount of starch, constantly stirring during solution. The solution, which at first was turbid, will become perfectly clear except for a faint opalescence. It is best prepared fresh, for after two or three days fine flakes will separate out, and it is then useless.

(3) 1 per cent. NaCl solution.

(4) $\frac{1}{50}$ N iodine solution in distilled water. This deteriorates after a time, so it is better to have a $\frac{1}{10}$ N solution and dilute as required.

The Test. A series of test-tubes is filled with decreasing amounts of urine. If two urines are to be compared, two series are taken, the corresponding tube in each series being filled with the same amount of urine. Each tube is marked with a grease pencil showing the amount of urine it contains. It has been found that the most convenient series for ordinary cases is represented by a row of ten tubes for each specimen of urine. The tubes are filled as follows:

Tube No.	Urine c.c.
1	0·6
2	0·5
3	0·4
4	0·3
5	0·2
6	0·1
7	0·09
8	0·08
9	0·07
10	0·06

For measuring these quantities a 1 c.c. pipette is used which is graded in hundredths. By this means it is easy to measure the amounts from 0·6 to 0·1. For the smaller quantities one must work with a $\frac{1}{10}$ dilution with NaCl. The amount of fluid in each tube is made up to 1 c.c. by the addition of NaCl.

2 c.c. of the 0·1 per cent. starch solution is added to each tube, and the contents carefully shaken. In adding the saline and starch solutions it will be found convenient to have two burettes, a 10 c.c. for the NaCl and a 25 c.c. for the starch, each c.c. of the small burettes being divided into tenths. The series of tubes is then placed in a water-bath for half an hour, which is kept at a temperature of 38–39° C. by means of a thermo-regulator. At the expiration of that time they are all taken out and placed in cold water for two to three

minutes to stop the ferment action. They are then arranged in their original order in the test-tube stand (one with a double tier is convenient when comparing two urines), and to each tube one drop of the iodine solution is added. It is now ascertained which tube, beginning from No. 1 or that containing 0·6 c.c., is the first to show a blue tint. This is taken as the 'limit' tube, or in other words the tube in which the first trace of undigested starch is found, and from this the diastase content of the urine can be calculated, as shown below. In adding the iodine to the tubes it must be noted that in those tubes which contain a relatively large amount of urine the colour produced by the addition of one drop of iodine disappears almost at once, so that it will be found necessary to add more than one drop; but in comparing two urines the same amounts must be added to the corresponding tube in a parallel series. Should an excess of iodine be accidentally added, the first trace of blue colour will be obscured by a brownish tinge. However, this colour can be restored to its proper place in the series by adding about another c.c. of saline.

The results of a series from a normal case are here shown in a tabular form:

Tube No.	Containing		Iodine.	Colour.
1	0·6 c.c.		1 drop	yellow
2	0·5 „		„	„
3	0·4 „	All made up to 1 c.c. by	„	„
4	0·3 „	addition 1 % NaCl. Then	„	red yellow
5	0·2 „	2 c.c. 0·1 % starch solution	„	„ „
6	0·1 „	added, and all incubated	„	mauve 'limit'
7	0·09 „	for half an hour at 38–39° C.	„	dark violet
8	0·08 „	Cooled, and iodine added.	„	„ „
9	0·07 „		„	blue „
10	0·06 „		„	„

In this case we see that the tube containing 0·1 c.c. of urine is the 'limit', or in other words all the starch has been digested with the formation of erythrodextrin in the tube containing 0·2 c.c. The calculation is then easily made.

0·2 c.c. urine will digest 2 c.c. 0·1 per cent. starch solution in half an hour.

$\therefore$ 1 „ „ „ „ $\frac{20}{2} = 10$ c.c. „ „ „ „

This result can be expressed as the figure:

$$d\frac{38^\circ}{30'} = 10,$$

or more simply:

$$d = 10 \text{ units.}$$

In the twenty-four hours' test the operations are similar, but the solutions used are different. The urine measurements are the same, and are made up with 1 per cent. saline to 1 c.c. A 1 per cent. solution of starch is used and 5 c.c. of this are added, and the mixture incubated at 38–39° C. for twenty-four hours. At the end of this time the tubes are taken out, cooled, and all filled up with tap-water to within an inch or two of the top. One or more drops of $\frac{1}{10}$ N iodine solution are added, the colours compared, and the calculation worked out in

a similar manner to the half-hour test. The figures would of course be higher than in the half-hour test. For example, if, as in the above table, the tube containing 0·1 c.c. urine was found to be the limit, the calculation would be :

0·2 c.c. digests 5 c.c. 1 per cent. starch solution in twenty-four hours,

$\therefore$ 1 „ „ $\frac{50}{2} = 25$ c.c. „ „ „ „

Wohlgemuth here uses the figure :

$$D\frac{38^{\circ}}{24 \text{ hr.}} = 25,$$

or : $D = 25$ units,

the letter D being used to denote the higher strength of starch solution.

As has been already stated, the half-hour test is far simpler, has been more generally used, and is just as reliable, so that all the results will here be quoted in terms of *d*. We shall then have as the value of *d* one of a series of figures, each corresponding with a tube containing a certain fractional amount of urine upon which the calculation is based. Taking therefore a series of tubes containing 0·6–0·01, we shall have the corresponding series of figures in harmonic progression.

Urine.	*d* value.	Urine.	*d* value.	Urine.	*d* value.
0·6	= 3·3	0·09	= 22·2	0·03	= 66·6
0·5	= 4	0·08	= 25	0·02	= 100
0·4	= 5	0·07	= 28·5	0·01	= 200
0·3	= 6·6	0·06	= 33·3	and so on.	
0·2	= 10	0·05	= 40		
0·1	= 20	0·04	= 50		

Glancing at these figures, it is obvious that the method can have no claims to extreme accuracy as to the exact amount of starch digested by 1 c.c. of any given urine. On the other hand, as will be shown later, the *d* value for any given twenty-four hours' specimen of normal urine keeps so closely within certain limits that for clinical purposes no greater accuracy is required.

Again, the figures show wide differences at certain points in the series, e. g. between 10 and 20, and here it frequently happens that one is able to guess if the real figure lies between these two. With a little practice one is soon able to form a mental picture of the exact shade of mauve which should be displayed by a tube containing the first trace of unaltered starch, and so if, for example, the tube containing 0·1 c.c. is a red yellow, while that containing 0·09 c.c. is blue or a much deeper mauve than one expects to find in a 'limit' tube, then one is justified in assuming that the real figure lies between 10 and 20. On the other hand, when the differences between the figures are small, so is greater care needed to pick out the first mauve tube.

Daylight is better than artificial light, though if the tubes are viewed against dead-white paper, it is not essential. I have usually kept under toluol a urine a certain known volume of which will produce the standard mauve tint ; this can be used as a control if required.

The results of animal experiments led Wohlgemuth to the conclusion that although there were sometimes appreciable fluctuations in the quantities of urine produced, the amounts of diastase excreted were approximately equal on the right and left sides. This equality, however, persists only so long as the urine excreted by one ureter is compared with that secreted by the other ureter over the same period. On the other hand, if the activity of the kidneys is interfered with by the injection of some irritating substance, a great irregularity in the excretion will occur.

Caspar and Richter (4), from their experiments on normal human beings, contend that, if in performing double ureteric catheterization care is taken to see that catheters of equal width are used and kept clean, both kidneys will, if normal, furnish in a given time almost exactly the same quantity of urine, and that the specimens of urine from either side will have the same molecular concentration as indicated by the freezing-point method.

Wohlgemuth (25) gives a list of normal persons upon which double ureteric catheterization was performed, in whom disease was suspected but none found. The results of the phloridzin, indigo-carmine, and freezing-point tests are in most cases noted, as well as the diastase values.

In all normal cases the diastase concentration was exactly the same on the two sides. Further, that the values for d varied between 6·6 and 25, unless there was pronounced polyuria, when a lower reading would be given. This is in accordance with my own observations on twenty-four hour specimens in healthy subjects, except that a figure as high as 33·3 is occasionally found in an apparently normal case, though such an experience is rare. On the other hand, if one examines single specimens where the urine is, judging by its colour, more concentrated than usual, a reading of 40 is occasionally met with; but I have never found a higher reading than this in a healthy person.

Wohlgemuth (25) gives the results of a large number of experiments which all show that a kidney whose functional capacity is damaged secretes less diastase than a normal kidney, and he is of the opinion that this test is simpler, if not more accurate, than the other tests that have been devised for the same purpose.

He gives the results from one case of nephrectomy showing a gradual improvement in the efficiency of the remaining kidney.

Rosenthal (17) is among the most recent of those who have investigated this subject. He examined twenty-four hour specimens of urine from a large number of different cases by Wohlgemuth's half-hour test. His method of stating the results is, however, different. He multiplies the daily excretion by that quantity of urine which has digested the starch.

e. g. Daily quantity 1,500 c.c.,

0·2 c.c. digests 2 c.c. 0·1 per cent. starch solution,

$\therefore$ the absolute diastatic strength $= \frac{1500 \times 10}{2} = 7500.$

Hence percentage concentration = 500 per cent.

There seems to be no advantage in using this method. Rosenthal claims that by this means it is possible to compare the results obtained by different observers, and that the *d* strength of 1 c.c. urine according to Wohlgemuth's calculation is not identical with the *d* strength of the patient. But Wohlgemuth has himself pointed out that the *d* value of the urine of any given person varies at different times during the day, therefore it is clear that the test must be carried out with a twenty-four hour specimen; also that the value of 1 c.c. of this urine can be taken as representing the average value of the urine excreted by any given individual. Rosenthal's method only results in a cumbersome series of figures, which are the ordinary series of Wohlgemuth multiplied by fifty, or, in other words, half the real percentage. As regards his figures for the 'absolute diastatic strength', the results would vary out of all proportion to slight changes in the daily excretion, so that it seems simpler to calculate by the Wohlgemuth method, verifying the accuracy of the figures by noting whether there is pronounced polyuria or the reverse. It will be seen later that it requires a considerable variation in the total amount excreted before the figures for diastase undergo much alteration.

In quoting Rosenthal's results, therefore, the ordinary values for *d* are used. He finds that in normal cases the average value for *d* is 10, that a diminution in the secreting power of the kidney means a diminished ferment output. In acute infective fevers there is a rise which falls immediately on the appearance of nephritis. In diabetes mellitus the value is always low or absent.

In a recent paper Rosenthal (18) has examined the urine of a series of cases of diabetes insipidus and finds that diastase is always absent in this condition, and further that proteolytic ferments are rarely found.

Wohlgemuth and Noguchi (22) have carried out experiments in dogs with a view to ascertaining whether it is possible by examining the diastase content of the urine and serum to diagnose a case of suspected injury to the pancreas in the human subject. Wohlgemuth has shown that the amount of diastase in the blood increases after the resection of a portion of the pancreas in dogs. He suggested that this was either due to the escape of the pancreatic secretion into the blood or to the congestion of secretion behind the sutures leading to an abnormal amount being taken up by the blood. They cut through the pancreas of a dog under morphia-ether narcosis, stopped the bleeding, and closed the abdomen. The diastase estimation was carried out by Wohlgemuth's method, the test for the serum being performed in a similar manner to that for the urine. Blood samples were taken before the operation and at every succeeding hour. The diastase value rose from 80 to 200 in four hours, to 332 in six hours, to 800 in twenty-four hours, and to 1,600 in forty-eight hours. That for the urine rose correspondingly. In another experiment a small cut was made in the pancreas and this organ was slightly bruised by the fingers. Here the value rose from 40 to 62·5 in four hours, and eventually to 160 in forty-eight hours. They then examined a number of human sera and found that the average diastase value under normal conditions was between 8 and 16, and that the highest normal

value was 32. It would, therefore, seem likely that if in a case of a stabbing wound of the abdomen the diastase value of the blood is found to be over 32, the deduction that there is a wound of the pancreas would be justified. They found that this raised value is maintained for seventy-two hours after the infliction of the wound and even as long as ninety-six hours.

No special investigation was made as to the nature of the ferment except to show that it would hydrolyse starch to maltose, nor were any experiments made as to the action of electrolytes. One might expect that the salt content as well as the reaction of the urine would considerably modify the velocity of the reaction. Cole (7), working with a pure solution of ptyalin, shows the influence of various simple electrolytes upon its action on starch. He points out that the effect of any electrolyte on the rate of action of the ferment is compounded of two factors, the acceleration due to anions other than hydroxyl ions and the depression due to kations and hydroxyl ions. The influence of any electrolyte can, however, only be accurately studied in a pure solution of ferment, so that in such a chemical complex as the urine it would be a very difficult matter to determine the amount of balancing that must take place between the ions of the various electrolytes.

As stated, Wohlgemuth was unable to find any influence exercised by the salt content or the reaction of the urine. I have obtained high d readings from strongly acid as well as alkaline urines, and the presence of bacteria in considerable numbers, whether of the coli or putrefactive group, did not apparently produce any abnormal results.

The following experiments were made to confirm the presence of a starch reducing ferment in the urine:

1. Boiled urine has no reducing power.

2. When heated to 60° C. the ferment will gradually be destroyed, but it needs about forty-five minutes of this temperature before destruction is complete.

Experiment. A urine whose d value was 40, i. e. where the tube containing 0·04 c.c. was mauve to iodine after digestion, was heated at 60° C. At five-minute intervals 0·2 c.c. was drawn off, made up to 1 c.c. with saline, 2 c.c. 0·1 per cent. starch added, and the mixture digested as usual:

The portion taken after	5	minutes	was	light yellow	to	I	after digestion.
„	„	10	„	light yellow	„	„	
„	„	15	„	dark yellow	„	„	
„	„	20	„	reddish mauve	„	„	
„	„	25	„	mauve	„	„	
„	„	30	„	violet	„	„	
„	„	1 hour	„	blue	„	„	
Also 1·0 c.c. urine „		1 hour	„	blue	„	„	

This shows that in twenty minutes the d value had fallen from 40 to 6·6, but the fact that the thirty minute specimen was violet showed that there was

still some ferment remaining. After one hour there was no trace of any alteration to the starch however much urine was taken.

3. It is not usually possible to get a copper reduction in an ordinary series from the tubes which are colourless to I after digestion, either because of the small amount of maltose present, maltose having a feebler reducing power than dextrose, or because the starch conversion has not proceeded as far as the maltose stage.

Experiment. 10 c.c. of urine having a *d* value of 10 were added to 50 c.c. 1 per cent. starch and the whole digested at 38° C. for two hours. A portion of this fluid, when tested with Fehling, gave a slight reduction, but after evaporation to about 10 c.c. the residual fluid gave a reduction that was complete.

It was noted that a strong solution of soluble starch would itself partly reduce Fehling's solution, producing the red suboxide.

4. After several attempts which failed owing to the incubation period being too short, an osazone was obtained from a digested mixture.

Experiment. The solutions taken:

A. 20 c.c. urine *d* value, 10 + 40 c.c. 1 per cent. starch solution.

B. 20 c.c. boiled urine „ + 40 c.c. „ „ „

C. A 1 per cent. solution of starch boiled.

These were put in separate flasks, and phenyl hydrazine and sodium acetate added to each in the proportion of 1 to 2. A was well shaken up with toluol to prevent any fermentation occurring, B and C being sterile. They were then all incubated for seventy-two hours at 38° C. At the end of this period an osazone similar to maltosazone was found in A, but none in B or C.

5. The ferment can be extracted from the urine with alcohol.

Experiment. 9·5 c.c. of a urine having the high *d* value of 400 were placed in a flask and 50 c.c. absolute alcohol added. A fairly dense precipitate formed, which contained besides the chlorides, sulphates, phosphates, &c., a small amount of albumin. The mixture was allowed to stand for two days, and was occasionally shaken. It was then filtered. The residue was partly dried on the filter paper, which was then soaked in 25 c.c. of 1 per cent. saline for one hour. The paper was then removed and the remaining adherent precipitate scraped off into the saline. This was then filtered. A preliminary experiment having shown that the ferment was present in the filtrate, a series of tubes was prepared containing 0·6 c.c. down to 0·01 c.c. It was then found that the *d* value of the filtrate was 25. In other words, one had extracted from the original urine a liquid which, when made up to the original volume, would have a value of 65, for the ferment extracted from 9·5 c.c. urine was diluted with 25 c.c. saline or 1 in 2·6.

No precautions were taken to obtain extreme accuracy, it being sufficient to prove that a considerable quantity of the ferment could be thus extracted.

The original alcoholic filtrate was next examined to see if there were any traces of ferment remaining therein. The alcohol was evaporated at 38° C., and the residue made up to 9·5 c.c. with saline. This was heated as follows:

1 c.c. + 2 c.c. 0·1 per cent. starch,
1 c.c. + 1 c.c. 0·1 per cent. starch,

placed in two test-tubes and digested for half an hour.

With the addition of iodine a deep mauve colour appeared in each case, differing slightly from a similar mixture which was not digested. In the latter the colour was a distinct blue and was more permanent than in the digested mixture. One may, however, assume that practically all the ferment was precipitated by the alcohol, but it is easy to see how by this method a certain amount could be lost, possibly by the formation of some adsorption compound with the precipitated proteins.

6. In order to form some idea of the comparative concentration of the ferment in the urine, human saliva was tested by a similar quantitative method. 1 c.c. of saliva was added to 9 c.c. of 1 per cent. saline, and the mixture thoroughly shaken. From this dilutions of $\frac{1}{100}$, $\frac{1}{1000}$, $\frac{1}{10000}$ were prepared, a series of tubes taken and digested with starch as usual. It was then found that the first tube to show a mauve colour with iodine was that containing 0·1 c.c. of the $\frac{1}{10000}$ dilution, that containing 0·2 c.c. being cherry red. In other words, 2 c.c. of 0·1 per cent. starch were digested by 0·00002 c.c. of saliva in half an hour.

$$\therefore d = 100{,}000.$$

The Influence of Diet on the Output of Diastase.

The ordinary variations in hospital food from milk to full diet did not appear to have much influence on the output. Nor, as far as could be seen, did the substitution of a carbohydrate free diet in diabetes produce any marked change. High readings were found in patients on full diet as well as in those on milk only. There is one experiment, however, of interest in this connexion. The urine of an infant aged nine months was examined, who had never received starchy food of any kind, but had been fed on milk only. On three successive days estimations were made on specimens passed during the morning, afternoon, and evening, and the d value varied between 3·3 and 4.

The next day,

Jan. 30, a small feed of Allen and Hanbury's No. III food (containing some unaltered starch) was given at 2 p.m.
At 6 p.m. $d = 6{\cdot}6$.

Jan. 31. Morning $d = 4$.
Similar feed at 2 p.m.
4.30 $d = 5$.
6.30 $d = 6{\cdot}6$.

Feb. 1. Rather larger feed at 2 p.m.
2.30 $d = 5$.
3.30 $d = 10$.
5.30 $d = 5$.

Feb. 5. Morning $d = 4$.
Similar feed at 2 p.m.
4.30 $d = 10$.
6.30 $d = 10$.

Feb. 12. Two meals of starch-containing food per day,
evening $d = 20$.

From the above results it seems likely that, as is known to occur in the type of experiment initiated by Pawlow, an increasing quantity of amylolytic ferment is secreted by the organism in response to the administration of food containing starch.

The experiments were made with great care in view of the possibility of the alterations being but slight, but the results were definite and most striking. Further experiments on children might possibly yield interesting results as to whether any given case is dealing properly with starch-containing foods.

Diastase in the Blood.

A few experiments only were made in this direction. As cited above, Wohlgemuth and Noguchi (22) working with dogs showed how a rise in the diastase content of the blood corresponded with an equal rise in the urine, and one might reasonably suppose that, granted the kidneys are healthy, a similar state of affairs would occur in man. On the other hand, if the efficiency of the kidneys is impaired by nephritis, it might be that the diastase content of the blood would rise above that of the urine. But we are still in ignorance of several factors that might be concerned in these questions, such as the rate at which the ferment is absorbed into the blood or excreted by the kidneys, and so one is hardly justified in comparing the diastase value of a small sample of blood with that of a twenty-four hour specimen of urine.

It was found that the values obtained from the serum were a little higher than those from the plasma.

Technique. The amounts of serum available being comparatively small, a different method was used for the estimation. For the unit of volume a mark was made on a Wright's pipette, and there was no practical difference in the results, whether equal volumes of serum were digested with increasing volumes of starch or whether equal volumes of starch were used with decreasing volumes of serum. The former method is more convenient and requires less serum.

The amount to which the serum is diluted depends upon the extent of accuracy required in the results. The average reading for normal serum was found to be about 10, which corresponds well with Wohlgemuth's figures of 8–16. Therefore, if only a rough estimate is required, the serum can be diluted $\frac{1}{10}$, but for ordinary purposes $\frac{1}{5}$ is better.

A series of small glass tanks made out of tubing are taken and marked 1, 2, 3, &c., according to the volumes of 0·1 per cent. starch solution to be added to each. The serum is diluted as required with normal saline, and the series is completed so that each tank contains one volume of diluted serum and an amount of starch solution as indicated by its mark. They are then all capped with plasticine, placed in a water bath at 39° C., and incubated for half an hour. At the end of this period they are taken out, arranged in series, the caps are removed, and a small drop of $\frac{1}{50}$ normal iodine solution added to each. It is then noted which tank first shows a trace of blue colour, and the calculation is

made from that preceding; e.g. Serum diluted $\frac{1}{5}$; tank containing 4 volumes of starch + 1 volume of diluted serum gives first trace of blue colour,

$$\therefore d = 15.$$

Experiment. Comparing the values of serum and plasma.

A. Normal serum = 15
„ plasma = 10 } urine = 10 to 20.

B. Diabetic serum = 15
„ plasma = 10 } urine = 6·6. Over 100 oz. passed per day.

In A the values for blood and urine correspond fairly well. The serum and plasma were made from the same sample of blood. The plasma was obtained by mixing one volume of blood with four volumes of citrated saline, centrifuging and pipetting off the clear plasma. The other experiments with serum will be given with the cases as they occur.

. . . . . .

In choosing the cases for investigation by this method the following plan was adopted. In the first place, those conditions which had already been examined by other observers were investigated; secondly, those which had not already been worked out in detail as regards their clinical course; and, lastly, a search was made among a variety of conditions with the hope that readings at one or other extreme of the scale might serve to establish the test as an aid to diagnosis.

As regards the urine from normal cases it was noteworthy how closely the values for diastase kept within definite limits. Providing the test was made on a twenty-four hour specimen of normal concentration, say about 50 oz. in the twenty-four hours, the values were rarely below 6·6 or above 25. For this reason twenty-four hour specimens were examined wherever possible. Where such were not available, although the diurnal variation could not be shown so accurately, single specimens were found to be of sufficient value for clinical purposes, for, as has already been mentioned, neither higher readings than 40 nor lower than 5 have occurred in a single specimen of any normal case. Therefore, if readings are found above or below these limits, it can be assumed that the case is pathological.

If the total amount secreted in the twenty-four hours is known, one can form some idea as to whether the concentration is affecting the result, granted one may assume that a certain definite amount of ferment is secreted daily. For example, supposing the reading is 20 when 50 oz. are excreted, then, if only 25 oz. were passed daily, one would not be surprised at finding a reading of 40; similarly, if there were considerable polyuria totalling 200 oz. or more, a reading of 5 could not be considered unduly low. This point has been noted by Rosenthal when he speaks of the absolute diastatic strength, as has already been mentioned, but it will be shown that in these cases, where the test might be of value from a diagnostic point of view, the variation from the normal is so large as practically to be unaffected by the question of concentration.

Cases.

Differential diagnosis, and test for functional activity.

I have only one case to record similar to those in Wohlgemuth's series.

I. *Tuberculosis of right kidney.*

Ureteric catheterization. One catheter was passed into the left ureter, but as the right was occluded, the other was left in the bladder. Urine from the left ureter filled three test-tubes full in three hours, while that from the bladder, i.e. from the right kidney, only filled half test-tube in the same time. There was blood in both specimens, but that from the bladder was deeply tinged.

Feb. 24. Right side, $d = 10$; left side, $d = 40$.

Here it should be noted that, in spite of the presence of a large amount of blood in the specimen from the right kidney, the value was considerably lower than that from the left kidney, showing that its functional activity was much diminished, while on the other hand the left kidney was acting well. The right kidney was removed on Feb. 25, and was extensively diseased.

Feb. 26. Twenty-four hour specimen, $d = 50$.

A similar figure was recorded on Feb. 27, but unfortunately no further specimens were obtained. The patient was, however, discharged perfectly well.

As to the influence of the contained blood upon the reading found from the right kidney specimen, an experiment was made. To a urine free from blood having a value of 10, a small amount of fresh blood was added until its colour was approximately the same as the right kidney specimen in the above case. Its value was raised by this process to 22·2, showing that in all probability the real figure for the right kidney specimen was 5 or less. The left kidney specimen, being less blood-tinged, would be correspondingly less affected.

II. *Nephritis.*

Here, in common with other observers, my cases show low readings in cases of acute and chronic nephritis.

1. Chronic nephritis. Acute attack three months previously.

Average amount excreted per diem, 35–40 oz.

Albumin averaged about $\frac{1}{4}$.

Jan. 18.	$d = 4$	Feb. 14.	$d = 4$
„ 25.	$d = 3{\cdot}3$	„ 20.	$d = 4$
Feb. 6.	$d = 2$	Mar. 24.	$d = 5$.

Discharged from hospital improved.

2. Chronic nephritis, interstitial.

Average amount excreted per diem varied between 40 and 90 oz., occasionally sinking considerably below this.

Jan. 18.	6·6	Amount excreted =		42 oz.
„ 25.	6·6	„	„	51 „
Feb. 14.	Nil	„	„	10 „ (?)
„ 20.	Nil	„	„	94 „

Discharged from hospital improved.

Judging from this case the amount excreted per twenty-four hours does not affect the d values.

3. Recovering from acute nephritis.

Aug. 16. d = nil. Aug. 18. $d = 4$.

4. Chronic nephritis. Tendency to uraemia, sickness, and headaches. $d = 10$.

5. Chronic nephritis, exacerbation one week previously. Left kidney removed after accident $8\frac{1}{2}$ years previously. Alb. = $\frac{1}{2}$ on boiling. $d = 10$. 40 oz. passed.

This case progressed favourably, and is interesting in showing how a single kidney can stand the strain of an acute attack.

6. Chronic nephritis.

Feb. 4. $d = 2{\cdot}5$
„ 11. $d = 2{\cdot}8$
„ 20. $d = 2{\cdot}8$.

7. Chronic nephritis. High blood pressure. Albumin never more than a trace. Retinitis with oedema of disks. Headaches.

Jan. 18. $d = 22{\cdot}2$
„ 25. $d = 20$
Feb. 14. $d = 25$
„ 20. $d = 10$. Urine distinctly blood-stained.

8. Chronic nephritis with considerable oedema.

Sept. 16. $d = 20$
„ 19. Paracentesis. Ascitic fluid had a d value of 3·3.
„ 25. $d = 20$.

Several other similar cases of chronic nephritis were examined on single occasions with results that varied between 6·6 and 20.

9. The d values of the serum and urine compared in a chronic parenchymatous and a chronic interstitial nephritis.

A. Chronic parenchymatous.		B. Chronic interstitial.	
Urine.	d = between 6·6 and 10.	Urine.	$d = 10$.
Serum.	d = between 5 and 10.	Serum.	$d = 25$.

There was a considerable amount of albumin in A, and only a trace in B. The above cases are inconclusive, and further work is needed to explain certain anomalous results. We see that in certain cases of renal disease low readings are found, whereas in others they are normal. In one case of clinically pure interstitial nephritis the ferment was absent on two occasions. This is in accordance with Rosenthal's observations, for he found that the chronic interstitial form gave consistently low readings. If the kidneys are so damaged by disease that they are unable to excrete the diastase normally present in the blood, one would expect the amount of ferment in the blood to increase, and that we should have a higher d value in the serum than in the urine. In example 9 above we see that this occurred in B, but that in A the values were nearly the same, whereas clinically the cases were of about equal severity. Later, I shall hope to show that this apparent fallacy is due to the different forms of nephritis concerned, that where the kidneys are permeable to albumin they are also permeable to ferment. Therefore, applying the test to cases of nephritis in general as a means of estimating the amount of damage to the kidneys, the d values for the urine should be compared with those for the serum. Where albumin is scanty or absent, the serum-urine ratio might be taken as a direct measure of the damage. In other words, if the d value of the serum is consistently higher than that of the urine, we might conclude that the secretory activity of the kidneys is impaired, and should this occur also when much albumin was being passed, it would mean that the damage was even greater.

III. *Diseases of the Pancreas.*

In view of Wohlgemuth's work one would expect to find that in pancreatic lesions there might be an increase of diastase in the urine. The following cases throw some light on this point:

1. Carcinoma of head of pancreas. On admission to the hospital, the patient was very jaundiced, and the liver was enlarged, reaching to the umbilicus.

These are not twenty-four hour specimens, but were all taken in the morning.

Aug. 12. $d = 33{\cdot}3$ Bile + +
„ 13–19. Between 66·6 and 100.

Operation. Cholecystenterostomy. Gall-bladder empty. Carcinoma of the head of the pancreas found.

Aug. 22. $d = 50$
„ 27. $d = 66{\cdot}6$ } Patient much weaker and losing flesh.
„ 29. $d = 100$ }
Sept. 20. $d = 400$. Very emaciated.

The patient was then discharged from hospital, as nothing more could be done.

Here the readings were consistently above normal, that for Sept. 20 being comparatively enormous.

2. Miliary tuberculosis. Boy aged 14. No pancreatitis suspected during life.

Aug. 16. $d = 400$
„ 18. $d = 222{\cdot}2$
„ 23. $d = 200$.

Death occurred shortly afterwards. At the post-mortem there were miliary tubercles all over the abdominal cavity, and a caseous gland was buried in the pancreas.

A section of the pancreas showed marked increase of fibrous tissue, destruction of the islands of Langerhans, and some fatty changes. No tuberculous deposits were seen in the pancreas in the section.

It would appear that a diffuse interstitial pancreatitis is more commonly associated with tuberculosis of other organs, and it has been suggested that this form of chronic pancreatitis may be caused by chemical products elaborated in a tuberculous lesion.

This case is interesting in that the examination for diastase was made without any preconceived idea as to the existence of a pancreatitis. The persistent high readings led one to follow up the case to see if some pancreatic lesion might be present.

3. The patient came into hospital with persistent jaundice.

In July a cholecystenterostomy was performed, and at the operation the head of the pancreas was found to be enlarged, but there was no evidence of carcinoma. The jaundice gradually cleared up after the operation.

The daily quantity of urine was normal throughout, and no sugar was found until Oct. 2. No albumin present.

Aug. 2. $d = 285$ Aug. 8. $d = 200$
„ 7. $d = 100$ „ 12. $d = 100$.

Cammidge's test C., negative.

Aug. 16. $d = 500$. The highest reading in any of my cases.
„ 27. $d = 100$.

The patient was feeling much better, and the jaundice had quite cleared. He was sent to a convalescent home, but while there began to suffer from

diarrhoea and pains in the epigastrium, worse after meals. He passed an increased quantity of urine having to get up at night for the purpose. While away he gained 1 lb. in weight, but since returning home lost 3 lb.

He was readmitted to hospital on Sept. 28, and a fresh glycerine extract of pancreas was given three times daily.

Oct. 2. Urine s. g. 1015, faint trace of albumin, reduces Fehling. Presence of sugar confirmed by fermentation test, about 350 gr. per day. $d = 250$.

The patient, however, felt quite well and had no pain.

Oct. 6. Severe attack of vomiting. Temperature rose to 102° F. No jaundice and no diarrhoea.

Oct. 7. Temperature normal. Patient felt better. $d = 500$.

Oct. 14. $d = 285$.

The serum was also examined on this date and yielded a value of 50.

He was losing weight at the rate of over 1 lb. per week. Sugar was still present in the urine, 300–500 gr. per diem. The stools were examined for the proportion of neutral fats to fatty acids, and it was found that all the fat present, amounting to only 4 per cent., was neutral fat. This is remarkable, not only in the small amount of fat present, but that there should have been no fatty acid. Similar variations have, however, been found in pancreatitis, especially in the earlier stages of the disease (Robson and Cammidge (16)).

The patient shortly afterwards left the hospital, free from acute symptoms, yet notably weaker.

This case is noteworthy, in that no reading was ever found below 100, and that the amount of ferment in the serum was also considerably in excess of the normal.

Cammidge's test C. yielded a negative result, but Robson and Cammidge in their series (16) found a positive result in only four out of sixteen cases of carcinoma of the pancreas. It seems likely, then, that the test for diastase may be of value in the diagnosis of such cases.

4. ? Pancreatitis. Temperature 100°–103° F. Appetite bad. Melaena, which ceased later.

This case had been previously operated on for stone in the common duct; the gall-bladder was then found to be normal.

The amount excreted varied between 20–30 oz. per twenty-four hours.

Cammidge's test C., positive.

Amount of fat in faeces normal.

Aug. 12. $d = 100$. Aug. 13. $d = 222{\cdot}2$.

5. ? Pancreatitis.
Cammidge's test C., negative. $d = 10$.

6. ? Pancreatitis.
Cammidge's test C., negative. $d = 25$.

7. ? Pancreatitis.
Amount of fat in faeces = normal. $d = 20$.

8. Persistent jaundice. ? Pancreatitis.
Cammidge's test C., positive. Sept. 30. $d = 50$.
Stercobilin present, no bile or any other abnormality in the urine.

9. Chronic pancreatitis, with persistent jaundice.
Cammidge's test C., positive.

Oct. 24. $d = 66{\cdot}6$
d value of serum = 20
Oct. 27. $d = 100$.

10. Acute pancreatitis. Operation. Death.
From urine obtained post-mortem. $d = 66{\cdot}6$.

11. ? Carcinoma or pancreatitis. Persistent jaundice, with bile in the urine. Cammidge's test C., negative. $d = 6{\cdot}6$.

Of these eleven cases seven were those of undoubted disease of the pancreas, the other three being suspected cases.

The results can be thus summarized:

Case.	Cammidge's Test C.	*d* value of Urine.
Carcinoma of pancreas	not done	66·6–400
Chronic pancreatitis	not done	200–400
Carcinoma of pancreas	negative	100–500
Acute pancreatitis	positive	100–222·2
Suspected	negative	10
Suspected	negative	25
Suspected	not done	20
Chronic pancreatitis	positive	50
Chronic pancreatitis	positive	66·6–100
Acute pancreatitis	not done	66·6
Suspected	negative	6·6

These cases show that in cases of pancreatic disease the *d* values for the urine are, as far as can be seen, always above normal, and may reach a very high figure indeed.

IV. *Diabetes.*

The opinion of most workers on this subject is that in diabetes there is considerable diminution of the ferment content of the urine, and that it is occasionally absent. As far as values for *d* are concerned, my results are only occasionally in accordance with these observations. Out of nine cases examined, some of them frequently and on consecutive days, no diastase was found on two occasions. One case of diabetic gangrene gave a value of 2. The average for the other cases was between 6·6 and 10. It must be noted, however, that very large amounts of urine are passed and that any ferment present must be abnormally diluted, so that, if the total amount of urine excreted in the twenty-four hours is divided by a figure which would bring it within normal limits, the value for *d* would, when multiplied by this figure, be normal, or even above normal.

The following figures give a fair idea of the average readings found in diabetes when the case is under treatment:

i. Acetone and diacetic acid present throughout.

Date.	Amount passed per 24 hours in oz.	*d* value.	Remarks.
April 4	not 24 hour spec.	50	
„ 5	112	—	Patient rather sleepy
„ 6	162	5	Comatose. Infusion of sod. bicarb. intravenously. Distinct cloud of albumin in the urine
„ 10	132	4	No albumin. Sugar = 20 gr. per oz.
„ 13	160	10	
„ 15	124	10	Sugar = 24 gr. per oz.
„ 21 & 25	over 100	6·6–10	
May 1	„	10	Discharged from hospital improved.

The single observation of 50 on April 4 is noteworthy, for although it was not from a twenty-four hour specimen, such a reading is certainly above normal. Also there is a distinct improvement in the *d* value after the readings obtained on April 6 and 10, probably due to the kidneys recovering their efficiency after the damage sustained during the period of acidosis.

ii. Acetone and diacetic acid present throughout.

Date.	Amount passed. oz.	*d* value.	Sugar per 24 hours.	Remarks.
Aug. 2	Not 24 hour spec.	25		
„ 3	128 24 hour spec.	5	4500 gr.	Off potatoes
„ 4	196 „	6·6		„
„ 5	257 „	6·6	6000 „	Carbohydrate free diet
„ 7	191 „	4		Partial coma. Inf. sod. bicarb.
„ 8	91 „	6·6–10	2000 „	
„ 12	106 „	6·6	„ „	
„ 13	all over 100	6·6–10	„ „	Serum value = 15
„ 19	„	„	3000 „	
Sept. 5	„	5	„ „	
„ 9 & 16	„	10	4500 „	

Here, as in the first case, there was a distinct drop in the *d* value during the period of acidosis. It will be noted also that there is no apparent connexion between the readings for diastase and the amount of sugar excreted, nor again does a large amount of urine mean that the diastase content falls. On August 5, with a total excretion of 257 oz. the value was 6·6.

If we may assume that the amount of urine excreted per twenty-four hours in cubic centimetres multiplied by the *d* reading = a figure representing the 'total diastatic strength' (Rosenthal), it will be found that the total diastase is normal or a little above normal. For example, if we take the average amount secreted per twenty-four hours in this case as 160 oz. = 4,560 c.c. and the average *d* value as 6, we have a total value of 27,360 units. In a normal case where twenty-four hourly output = 1,500 c.c. and the average *d* value 10 to 20, we have a total value of 15,000–30,000 units.

iii. Male, aged 21. Considerable amount of diacetic acid and acetone present.

Date.	Amount.	*d* value.	Remarks.
Aug. 14	180 oz.		
„ 15	309 „	4	Strict diabetic diet except for one potato per day
„ 16, 18	150 „	6·6	
„ 24	over 100	5	
Sept. 20	„	6·6	

Abscesses now appeared on the thighs and back, and the patient was in a very weak condition.

Oct. 1. About 140. *d* = 3·3. General condition worse. Death ensued a few weeks later.

iv. A case where glycosuria set in after an abdominal operation.

Date.	Amount. oz.	*d* value.	Sugar. gr. per day.	Remarks.
Aug. 23		10	1000	Full diet
,, 27	31	6·6–10	900	Carbohydrate free diet
,, 28	25 ?	25	240	,,
,, 29	36	20	720	,,
,, 30	46	20	500	,,
,, 31	32	6·6	640	,,
Sept. 1	?	33·3	420	,,
,, 3	38	10	1000	,,
,, 4	52	10	820	,,
,, 5	51	6·6	820	,,
,, 6	48	10	700	,,
,, 7	50	10–20	580	,,
,, 9	59	10	1020	,,

Here the amount of urine excreted per twenty-four hours is small as compared with a true diabetes. The *d* readings remain normal and have no connexion with the amount of sugar excreted.

v. True diabetes. Acetone and diacetic acid present.

Date.	Amount.	*d* value.	Sugar. gr. per day.	Remarks.
Aug. 23	Not 24 hour spec.	0	6500	Full diet except potatoes and starchy puddings
,, 24	24 hour spec.			Carbohydrate free diet
,, 27	108 ,,	10	2040	,,
,, 28	70 ,,	10	1010	,,
,, 29	123 ,,	25	2020	,,
,, 30	? ,,	25	?	,,
,, 31	124 ,,	20	2040	,,
Sept. 1	126 ,,	20	1040	,,
,, 3	70 ,,	20	1080	,,
,, 4	72 ,,	25	1080	,,
,, 5	72 ,,	33·3	1020	,,
,, 6	90 ,,	20	1040	,,
,, 7	116 ,,	20	1020	,,
,, 9	94 ,,	10	1010	,,

This case shows a consistently high normal reading.

The treatment in all these cases was similar, namely, strict diet where indicated, rest in bed with an occasional course of opium or codeia. It is possible that untreated cases would show lower readings, but it is clear as against the findings of some other observers that it is by no means the rule to find a diminished output of diastase in diabetes.

The Pancreas and Diabetes.

It has been shown above that in certain pancreatic lesions there is an enormous rise in the output of diastase. One might expect to find therefore a similar state of affairs in some cases of true diabetes ; this has apparently never been found, a fact which is difficult of explanation. Modern opinion is by no means decided as to the relationship between the pancreas and diabetes, as evidenced by the morbid changes found post-mortem. Changes in the islands of Langerhans may be met with, as is well known, and Opie (14) considers that diabetes is peculiarly related to interacinar pancreatitis, as opposed

to interlobular, but a certain number of cases remain in which no lesion whatever has been found in the pancreas. The recent work of Starling and Knowlton (19) shows that in normal blood there is a hormone, elaborated by the pancreas, by the aid of which muscle is able to break up sugar, and that this hormone is absent in diabetic blood, but as to how far the absence of this body is associated with any primary morbid change in the pancreas, and whether the pancreatic changes found in diabetes are secondary, further evidence is required.

V. *Cirrhosis and other Affections of the Liver.*

It is known that the pancreas is frequently affected with an overgrowth of connective tissue in cirrhosis of the liver. In the *two* cases below, where a post-mortem was obtained, there was no pancreatic lesion visible to the naked eye.

1. Alcoholic cirrhosis, with jaundice.
   Urine. Bile present, no albumin. $d = 5$.
2. Alcoholic cirrhosis, with jaundice.
   Tapped several times. In a sleepy toxic condition before death. $d = 10$.
   Amount per twenty-four hours, 25 oz. P.M. No pancreatic lesion visible to the naked eye.
3. Jaundice (?), malignant.
   Urine. Bile + +, trace of albumin. $d = 5$.
   P.M. Cirrhosis of the liver, no evidence of malignant disease or of pancreatitis.

VI. *Catarrhal Jaundice.*

In those cases of catarrhal jaundice due to an ascending infection from the duodenum, it might be expected that there should be some obstruction to the flow of pancreatic juice as well as that of the bile, as the catarrhal process is most intense in the pars intestinalis of the duct, the ampulla of Vater being filled with mucus. Consequently there should be an excess of pancreatic ferments in the blood, and so in the urine, as has been found in cases of gross obstruction of the pancreatic duct (v. Benczur (1)). It is also known that Cammidge's test is frequently positive in such cases.

I have only one case to show of this type.

Acute catarrhal jaundice. So severe was the attack that at one time acute yellow atrophy was suspected. Cammidge's test C. was positive, and the d value lay between 66·6 and 100 at the height of the attack. There was much bile in the urine. Recovery was eventually complete, but unfortunately no more specimens were obtained.

On the assumption that any condition that prevents the normal amount of pancreatic juice reaching the duodenum will cause a rise in the diastase content of the urine, a series of cases of jaundice due to varying causes, with several estimations for diastase, might be of value in diagnosis as to whether the pancreatic duct were obstructed or not. In a case of cholelithiasis, granted the normal arrangement where the common bile and pancreatic ducts unite to form the ampulla of Vater, persistent jaundice with normal d readings might

well mean that the stone were situated at some distance up the common duct or in the hepatic duct, and similarly, if there were both jaundice and high d readings, the block might be said to be low down in the common duct or in the ampulla of Vater.

The association of jaundice with pancreatic disease, apart from gall-stones or any affection of the liver, is probably dependent upon the relation of the common bile duct to the duct of Wirsung and to the head of the pancreas. If the common duct lies behind the head of the pancreas, any disease of the pancreas may exist without the appearance of jaundice; if, on the other hand, it lies in a groove or is embedded in the head of the pancreas, either pancreatitis or growth must compress it and lead to jaundice. Robson and Cammidge (14) show that in 62 per cent. of their cases of chronic pancreatitis associated with cholelithiasis bile pigments were found in the urine before operation, and in 38 per cent. there was neither jaundice nor bile pigment in the urine. These figures, strangely enough, correspond with those for the anatomical variations described above.

In the cases of pancreatic disease described above, it is to be noted that the highest readings were found in carcinoma of the pancreas and chronic pancreatitis, where some measure of obstruction to the duct was likely.

VII. *Pregnancy.*

A series of pregnancies were next examined to see whether parturition was accompanied by any alteration in the d value of the urine. Normal and steady readings were found in all normal cases, and there was no change before or after parturition that could be said to be connected therewith. On the other hand, some of the cases of eclampsia examined showed most striking changes, characterized by a big rise during the eclamptic period, and a rapid fall to the normal as the case improved.

Case 1. Normal pregnancy.

Feb. 27.	Delivery.	Mar. 3.	$d = 20$
„ 28.	$d = 10$	„ 4 and 5.	$d = 10$
„ 29, Mar. 1.	10–20	„ 6.	$d = 25$
		„ 7.	$d = 10$.

Case 2. Normal pregnancy.

Thirteen consecutive examinations from Feb. 23 to Mar. 7 gave a constant series of readings between 6·6 and 10.

Mar. 7. Delivery.	$d = 5$
„ 9, 10, 12.	$d = 10$.

Case 3. Normal pregnancy.

Jan. 24 and 25.	$d = 10$	Jan. 31.	$d = 6{\cdot}6$
„ 26.	Delivery.	Feb. 4.	Nil.

Single observations on other normal cases gave results that were never above normal, the average being about 10.

Case 4. Normal pregnancy. Had eclampsia in Oct. 1910. *Accouchement forcé*, dead child. The albumin disappeared from the urine in three days.

March 31 and April 3.	$d = 10$.	Albumin absent.
„ 4.	$d = 25$	
„ 6.	$d = 28{\cdot}5$	
„ 8.	$d = 22{\cdot}2$	
„ 9.	$d = 20$	
„ 10.	$d = 10$.	Normal delivery.
„ 11.	$d = 33{\cdot}3$	
„ 17.	$d = 22{\cdot}2$.	Progress normal.

Case 5. Normal pregnancy. Eclampsia at last pregnancy.

April 16.	Normal delivery.	April 22.	$d = 28{\cdot}5$
„ 17, 18.	$d = 28{\cdot}5$	„ 24.	$d = 10$.
„ 20.	$d = 40$		

While no deduction is possible, it is interesting to note that, in view of the high readings found in eclampsia, both these cases gave values which, though within normal limits, were irregular, and on the whole above the average.

Case 6. Some albuminuria, but no toxic symptoms and no oedema.

Two determinations before labour.	$d = 10$
Seven days later.	$d = 10$.

Normal values were found in two other cases similar to the above.

The Toxaemias of Pregnancy.

Case 7. Albuminuria at the thirtieth week of pregnancy, with considerable oedema.

Date.	Amount per 24 hours.	Alb. by Esbach.	Urea.	d value.
Jan. 24	63	0·7 %	—	6·6
„ 26	91	0·2 %	—	6·6
„ 31	?	0·5 %	1·6 %	10
Feb. 6	24	0·75 %	1·4 %	10
„ 14	18	—	1·9 %	28·5
„ 16	18	—	1·52 %	28·5
		Natural Abortion.		
Feb. 17	18	0·45 %	—	6·6
„ 18	95	—	—	4
„ 19	108	0·1 %	—	5
„ 21	—	—	—	10
„ 28	—	—	—	10

The blanks indicate that there was no record. Progress was satisfactory. It is seen here that the d readings do not vary with the amount of albumin, but that there is a considerable rise in the former, together with the urea per cent., two days before abortion took place. That this rise in the d value is not necessarily connected with the small amount of urine passed, namely, 18 oz., is shown by the fact that on Feb. 17, when the amount was the same, the d value had fallen.

Case 8. Eclampsia. Coma. Incessant fits. Death without recovery of consciousness.

Catheter specimen during coma. $d = 40$.

The urine was clear and pale, and the wetting of the bed showed that it had been passed in considerable quantity.

Case 9. Eclampsia.

March 9. Catheter specimen taken just before labour. When half diluted, overloaded Esbach's tube. $d = 50$.

March 10.	$d = 25$.	Esbach 1·6 per cent.
„ 12.	$d = 5$.	Trace of albumin.
„ 14.	$d = 6·6$	
„ 16, 19.	$d = 10$.	Progress good.

Case 10. Eclampsia.

Feb. 3. Thirty-six hours after delivery, Esbach 0·5 per cent. Many casts. No blood. $d = 50$.

Feb. 6–14, inclusive. $d = 6·6$. Progress good.

Case 11. Eclampsia. Feb. 3. Catheter specimen taken before delivery by Caesarean section (living child).

Solid with albumin on boiling. Bile acids, leucin, diacetic acid, and acetone present; tyrosin absent. $d = 100$.

		Esbach.	Diacetic.	Acetone.
Feb. 4.	$d = 66·6$	0·2 per cent.	+	+
„ 5.	$d = 40$	0·025 „	+	+
„ 6.	$d = 50$	trace	+	+
„ 8.	$d = 40$	„	+	+

At this stage a severe attack of diarrhoea supervened, and no twenty-four hour specimen was obtainable for four days.

Feb. 12–14.	$d = 400$	trace	+	+
„ 16, 17.	$d = 200$	„	+	+
„ 21.	$d = 50$	„	none	none

Patient was discharged from hospital quite well.

We see here, as in the above cases, a high reading during the eclamptic period followed by a fall as the condition improved. The very high figures during the attack of diarrhoea are not easy of explanation. There could have been no obstruction of the common duct due to a spread of the general catarrhal conditions, for there was no jaundice. It is possible that there may have been a simple catarrh of the pancreas coexistent, but beyond the high figures for diastase no other evidence was present. It should be noted, however, that even when the patient was apparently quite well and was leaving the hospital, the figure was still above normal, so that, in view of the findings in known cases of pancreatitis, it is quite probable that the pancreas had been involved in the general toxaemia.

Case 12. Post partum eclampsia. Morning sickness throughout pregnancy.

June 15. Delivery. Twins.

„ 17. Six fits. Catheter specimen after fourth fit. Pale, acid. Distinct cloud of albumin. No acetone or diacetic acid. Temperature 100°–102° F. $d = 6·6$.

June 18.	Very restless. Temperature lower.	$d = 40$.	Amount	32+
„ 19.	One fit. Temperature normal.	$d = 10$	„	40+
„ 20.	No fits.	$d = 10$	„	42+
„ 21.	No fits. Albumin still present.	$d = 20$	„	23+
„ 22.	Better. „ „ „	$d = 40$.	Bacilluria	114+
„ 23.	„ „ „ „	$d = 100$	„	70+
„ 24.	Much better. No albumin.	$d = 100$	„	64+

The last three specimens were increasingly cloudy, due to the presence of B. coli.

June 25.		$d = 66{\cdot}6$
„ 27.	Urine less cloudy.	$d = 50$
„ 28.	Urine clearer.	$d = 50$.

Patient was discharged quite well.

The explanation of the sudden rise in the d value, starting on June 22, is difficult, occurring as it did at a time when the patient was rapidly improving. The presence of B. coli in the urine is without effect on its digestive power for starch, as was proved by an examination of other simple cases of B. coli bacilluria. Strangely enough, also, the rise was coincident with a very definite polyuria, namely, 114 oz. at least. There may have been an excess of ferment circulating in the blood, which was rapidly got rid of as soon as the kidneys recovered their normal efficiency, for the readings during the eclamptic period were low in comparison with the cases already mentioned, and their rise was almost synchronous with the disappearance of albumin from the urine.

Case 13. Eclampsia, one fit before delivery. When admitted she stated that she had had headaches and disturbances of vision for a few days previously.

March 31. Just before delivery. Alb. 0·4 per cent. No diacetic acid or acetone. $d = 6{\cdot}6$.

April 1 and 4.	Nil present.	
„ 6.	2·8.	No albumin.
„ 7.	6·6	„ „

Recovery was complete.

This case is in marked contrast to the foregoing. It would appear that in this instance the kidneys were damaged in some special manner, the readings found resembling those from a severe case of interstitial nephritis, for on April 6, although no albumin was present, the figure was only 2·8.

Case 14. A patient, at about the thirty-sixth week of pregnancy, stated that she had been suffering from attacks of giddiness while at home, and had had three fits shortly before admission to hospital. While in hospital no further symptoms appeared, and she was discharged after a few days. Wassermann's reaction was performed with a negative result. The d value of the urine from a twenty-four hour specimen was 250 on the only occasion it was examined, and so she was told to come up again a week later for another specimen to be taken. This yielded a value of 40. No further toxaemic symptoms had developed. She was admitted again a fortnight later when in labour, which was normal, and succeeded by a puerperium free from any complications. The child was healthy.

Before delivery.	$d = 6{\cdot}6$
One day later.	$d = 25$
Two days later.	$d = 25$

This case is interesting in that there was evidently some disturbance of a toxic nature while the patient was at home. suggesting the possibility of eclampsia supervening. This is further exemplified by the high d reading found. But it evidently soon cleared up, as there were no further symptoms, and the d values returned to within normal limits.

The following case shows the most severe form of the renal type of toxaemia:

Case 15. Oct. 6. Patient on getting up in the morning suddenly found that she was blind, and labour began. This was very prolonged owing to rigidity of the os. She was admitted to hospital in the evening, and a dead

5½ months foetus delivered by *accouchement forcé*. A catheter was passed and about 4 c.c. of blood-stained urine drawn off. This was solid with albumin, and after centrifugalizing to get rid of the blood, gave a d value of 3·3. In the eight days following, only about 2½ oz. of urine were passed, this mainly consisting of cellular débris resembling thin pus. There was not much oedema, a large amount of fluid being passed by the bowel.

On Oct. 14 the urine was still extremely scanty, and had a d value of 2·5. The serum examined on the same day gave a reading of 15, thereby showing, apart from other symptoms, that the renal damage was severe. Death occurred three days later.

Post-mortem, the whole of the cortex of both kidneys was completely necrosed and of a yellowish green colour; to the naked eye the change in the interstitial tissue was less plainly marked, but on microscopical examination degenerative changes were evident.

It is certain that in the toxaemias of pregnancy, the degree of damage to the kidneys varies considerably in different cases.

In this respect they can be divided into three classes:

1. Primarily renal type: either following the typical albuminuria of pregnancy, where the kidneys have been damaged for a comparatively long period, or as a more acute condition, such as Case 15.

Here we may expect low d readings, together with much albumin in the urine. The d value for the serum may exceed that of the urine.

2. Secondarily renal type: where there may be changes in the liver, and possibly in the pancreas, as in Case 11. The liver changes are shown by the presence of bile acids and leucin in the urine. There are also other evidences of disordered metabolism, such as the excretion of acetone and diacetic acid. Here, during the eclamptic period, there will be a large percentage of albumin in the urine together with high d values for the serum and urine.

3. Rare forms where there is no albuminuria, and where no recognizable changes can be found in the kidneys post mortem. In these cases the changes in the liver are most marked. It is not unlikely that there would be an excess of diastase excreted during the eclamptic period, associated with some pancreatic lesion.

Other toxaemias and acute infective conditions.

Case 1. Child, aged 3. Rash resembling measles. Headache and drowsiness. No discharge from eyes or nose. Koplik's spots absent. Temperature varied up to 103° F. Came down to normal about March 18. Acetone detected in the breath.

			Alb.	Diacetic acid.	Acetone.
Mar. 14.	2nd day of rash.	$d = 50$	trace	+	+
„ 15.	3rd „ „	$d = 250$	„	+	+
„ 16.	4th „ „	$d = 33{\cdot}3$	nil	+	+
„ 17.	5th „ „	$d = 66{\cdot}6$	„	+	+
„ 18.	6th „ „	$d = 40$	„	−	+
„ 22.	10th „ „	$d = 40$	„	−	trace
„ 29.		$d = 50$	„	−	„
April 8.		$d = 10$	„	−	− well
„ 12.		$d = 10$	„	−	− „

The return to normal values roughly corresponded to the disappearance of acetone from the urine. It was not decided whether or no this was a genuine

case of measles or whether the rash was secondary to the disturbance of metabolism evidenced by the acidosis.

Case 2. Child, aged 4. Post scarlatinal nephritis. Always subject to attacks of diarrhoea, with loss of appetite, accompanied by the appearance of acetone in the urine.

April 6. $d = 6{\cdot}6$. Alb. $\frac{1}{4}$, on boiling. Acetone +
„ 9 and 15. $d = 6{\cdot}6$ „ a little less. No acetone.

If there is any excess of diastase in the blood in such cases it is possible that owing to the loss of renal efficiency, due to the nephritis, the value for the urine would be low.

Case 3. Child, aged 2. Subject to frequent attacks of acidosis.
$d = 25$. Acetone +.

Case 4. Female, aged 25. Severe attack of acidosis, characterized by headache and sickness. Kept on starch diet and large amounts of sodium bicarbonate.

		Diacetic acid.	Acetone.	No alb. or sugar.
May 15, 19.	$d = 66{\cdot}6$	+	+	
„ 20.	$d = 28{\cdot}5$	+	+	
„ 21.	$d = 25$	−	+	
„ 22.	$d = 40$	−	−	
„ 23.	$d = 28{\cdot}5$	−	−	
„ 26.	$d = 25$			
„ 27.	$d = 40$. Patient quite well and on normal diet. The urine was not measured, but was passed in fair quantity and light in colour throughout.			

We have at present no satisfactory explanation of these 'acidosis' attacks in so far as they appear apart from any definite disease. They are fairly common among children, and are accompanied by headache, vomiting, and diarrhoea, with some rise of temperature. Still (21), referring to the recurrent pyrexia or the so-called 'bilious attacks' of children, suggests that they are the manifestation of some auto-intoxication allied to, if not identical with, that which produces recurrent vomiting. It seems not unlikely that an extreme form of all these conditions is to be found in the cyclic vomiting of children, for they are all amenable to the same form of treatment, namely, the withholding of food and the administration of large doses of bicarbonate of soda.

In Case 1 above, the d values were raised during the early stages of the attack, as is the case in most acute conditions, but the reading of 250 on the third day is so high as to suggest some catarrhal condition of the pancreas or its duct. Further investigation along these lines might throw some light on the pathology of these forms of intoxication.

Acute Infective Conditions.

A rise in d value up to 100 is met with occasionally, unless the acute infective process is attacking the kidneys themselves.

Case 1. Appendicitis, no sign of spreading peritonitis.
June 6. Temperature 102° F. Pulse 100–120. No operation.
$d = 50$. Amount 28 oz.
June 19. Temperature 99°. Pulse 92. $d = 20$.

Case 2. Appendicitis. General peritonitis. Death.

Aug. 6. Before operation. $d = 25$.
„ 8. Day of death. d = nil.

Case 3. Malignant endocarditis. Infarct of kidney. Blood, pus, and albumin in the urine. $d = 10$.

Case 4. Acute carbuncle. Septicaemia due to the Staphylococcus aureus. Purulent fluid in right knee-joint.

Sept. 16. $d = 66{\cdot}6$. 28 oz. passed.

Urine dark in colour, trace of albumin, a slight reduction of Fehling.

Sept. 19. $d = 100$. 28 oz. passed.
„ 25. $d = 66{\cdot}6$. Better, temperature lower.
Oct. 2. $d = 66{\cdot}6$. Death occurred some weeks later.

Case 5. Lobar pneumonia. $d = 40$. Death occurred two days later.

Case 6. Enteric fever. Temperature 102° F. $d = 10$.

Case 7. Caesarean section. Suppuration on fifth day.

Mar. 21. $d = 40$
„ 22. $d = 50$. Operation.
„ 25, 26, 27. $d = 33{\cdot}3$
April 5. $d = 66{\cdot}6$. Temperature rose, and was at its height on April 7; after that it gradually fell.
„ 6. $d = 100$
„ 8. $d = 66{\cdot}6$–100
„ 17. $d = 40$
„ 22. $d = 28{\cdot}5$
„ 24. $d = 6{\cdot}6$. Wound still suppurating a little, but patient up and about.
„ 30. $d = 20$
May 8. $d = 28{\cdot}5$. Wound healed.

Case 8. Acute pyelitis.

April 4. Rigor. Temperature 105° F. $d = 22{\cdot}2$.

Urine contained albumin, pus, and blood.

		Alb.	Pus.	Blood.	Temp.
April 8.	$d = 10$	−	+	−	normal
„ 15.	$d = 40$	+	+	−	
„ 17.	$d = 10$	trace	+	−	

These were single specimens only.

Case 9. Toxaemia due to acute suppurative nephritis. Woman four to five months pregnant. During life there was considerable doubt as to the diagnosis of this case, whether it was a toxaemia of pregnancy or a blood infection. The actual focus of the toxaemia was not discovered until after death, when at the post-mortem there were found multiple abscesses throughout the substance of the kidneys.

From April 23 to April 30, the patient was conscious, the temperature fluctuated between 101° F. and 104° F., and there was incontinence of urine, which appeared to be passed in considerable quantities.

Daily examinations for diastase from catheter specimens gave values between 6·6 and 10.

On May 1 the temperature was 104·6°, and the patient was evidently worse and practically unconscious. $d = 4$.

Until death, eight days later, there was no change in the d values, which

remained at about 6·6–10. Blood was present in the urine a few days before death. Pus cells were present, but there was no large amount of pus passed at any time.

From the above cases we can conclude that in acute infective conditions the figures for *d* may rise to 100, falling as the condition improves. The cause of this rise may in part be due to an abnormal concentration of the urine, but there is probably some other unknown factor concerned. Where the acute condition attacks the kidneys directly, no rise will take place, but the values will remain low, as in Case 9 above. Therefore, an explanation for the low or normal readings found in other cases, such as that of enteric, or that of general peritonitis, where the ferment was absent, may be given by assuming that the kidneys themselves have been damaged secondarily by the toxins.

The following miscellaneous cases were examined :

Graves' disease. Values between 6·6 and 10 were found in three cases examined on several occasions. In one case diacetic acid and acetone were present in the urine.

Pernicious anaemia. Similar values were found in two cases. They were not affected by an intravenous dose of salvarsan, which produced no appreciable reaction.

An idiopathic anaemia, not definitely pernicious, the chief symptoms being pain after food and no appetite. Four examinations yielded values varying between 40 and 100.

Carcinoma of Stomach.

1. ? Carcinoma of cardiac end, recent haematemesis. Readings between 10 and 20.

2. Carcinoma of lesser curvature, confirmed by laparotomy. Readings between 10 and 25.

3. Carcinoma of stomach, secondary growths in omentum, ascites requiring frequent paracentesis. Ascitic fluid gave value of 5. Urine 66·6 on several occasions.

4. ? Carcinoma of stomach. Losing weight, vomiting, &c. Readings about 6·6.

A case of ? pernicious vomiting in a woman four months pregnant. This so quickly ceased after admission to hospital, with no other treatment than rest and diet, that it was regarded as functional. The *d* value for the urine fell gradually in five days from 66·6 to 28·5, all vomiting ceasing two days after admission.

Normal readings also found in :

1. A case of colotomy for ulcerative colitis.
2. Henoch's purpura.
3. Senile gangrene. No sugar in the urine.
4. Cystitis due to B. coli.
5. Dilated stomach.
6. Disease of the posterior lobe of the pituitary body.

A pleural effusion free from blood gave a value of 6·6, and two ascitic fluids from cases of chronic renal disease readings of 3·3.

The values of d as a measure of renal efficiency.

It has, then, been clearly shown that in the normal individual the kidneys will eliminate from the blood a fairly constant quantity of diastase during the twenty-four hours, and that any damage to them will, by impairing their efficiency, reduce the output.

As regards the high readings found in various conditions, the explanation is not always so easy. If we may conclude that in certain forms of pancreatitis a considerable excess of ferment finds its way into the blood, then, if the kidneys are healthy, it will be rapidly excreted in the urine, and the values then found would be a measure of renal efficiency. On the other hand, high readings are found in eclampsia, where there is no doubt that in the majority of cases the kidneys have been severely damaged, as indicated by the large amount of albumin and casts present. That such damage is probably temporary is shown by the fact that albumin rapidly disappears from the urine after delivery has been effected. With one exception, where it remained as a trace (Case 11), little or none was found in my series after a week had elapsed from the time of delivery. In those cases that recover the extent of the damage can only be a matter of speculation, for in the excretion of albumin we have nothing more than a rough guide to the state of renal efficiency. A kidney may be just as badly damaged by an interstitial as by a parenchymatous nephritis, and yet the albumin may be present in considerable quantities in the latter while absent in the former. But still the fact remains that in certain cases we have a very high d value from a urine which has passed through damaged kidneys. It is not unreasonable to assume that in such cases it is a question of permeability, that the ferment simply comes through with the albumin separately, or as some form of adsorption compound without aid from the excretory activity of the cells through which it passes. For if the renal cells are permeable to the complex protein mixture, generally termed albumin, they should the more readily allow the passage of a simpler colloid such as diastase. In this sense, therefore, the d values are not a measure of renal efficiency.

Again, in chronic parenchymatous nephritis it is not improbable that a similar state of affairs exists. Cases where, from the general symptoms, there was clearly marked impairment of renal function, yet showed normal figures for diastase. Here the passage of albumin afforded a path along which the ferment could escape, and so the readings found were not a true measure of the extent of the damage sustained. On the other hand, if, as has been found by other observers, it can be shown that in pure forms of interstitial nephritis, with little or no albumin in the urine, there is a constantly low diastase output, then the readings can be taken as a more direct measure of renal efficiency, because the ferment has not the opportunity of escaping with the albumin.

As to whether the ferment is excreted by way of the glomeruli or the cells of the renal tubules, there is not at present sufficient evidence. If the quantity is much diminished in cases where the vascular lesions are most

marked, the injury to the tubules being slight, it could then be assumed that the ferment is excreted by the glomeruli. If it remains normal where there are considerable tubular and but slight glomerular changes, then it must either be excreted by the glomeruli or pass through the cells of the tubules with the albumin. A larger number of cases than at present on record would be needed to decide this point; as far as the evidence goes, it would appear that the glomerular path is the one taken, for where there is damage as in interstitial nephritis the values are low or absent.

Conclusions.

1. A starch-reducing ferment is excreted in the urine of normal individuals.

2. The amount passed per twenty-four hours is fairly constant, varying when measured by Wohlgemuth's short method between the values of 6·6 and 33·3 units, the average being 10–20. Each unit represents 1 c.c. of 0·1 per cent. starch solution converted into dextrine in half an hour by 1 c.c. of urine.

3. This ferment is also present in normal blood serum, which has, when examined by an equivalent method, an average value of 10 units.

4. This method of quantitative estimation is reliable, the values found in urine being unaffected by ordinary changes of diet in adults, by the reaction of the urine, the presence of bacteria, or any other abnormal constituent except blood. Nor is the activity of the ferment diminished to any important extent by keeping for many weeks, provided that the urine is preserved with toluol.

5. In an infant fed exclusively on milk, the amount of ferment excreted was very small. This rose at once with the administration of a starch-containing food.

6. An examination of twenty-four hour specimens of urine yielded results which can be divided into two main classes:

(*a*) As a direct measure of the efficiency of diseased kidneys;

(*b*) As a measure of the amount of ferment which has entered the blood.

As regards (*a*), certain reservations are necessary. It is probable that where there is a considerable amount of albumin passed, there is some leakage of ferment which has required no renal activity for its elimination, so that the values found might be misleading. Therefore, the diastase content of the serum should be also examined on more than one occasion, and the ratio of serum to urine compared. Where the *d* value of the serum constantly exceeds that of the urine, it may be assumed that there is a considerable loss of renal efficiency. Where the albumin is scanty or absent the values for the urine when compared with the normal can be taken as a more accurate indication of the amount of damage to the kidney, although here also observations on the serum as well would give more accurate information.

As regards (*b*), where the kidneys were undamaged and the ferment in the blood abnormally large the readings of *d* in the urine were much higher than those for the serum, showing that it is rapidly eliminated by healthy kidneys.

Such readings can be taken as a measure of the amount of ferment which has entered the blood. At the same time, in certain cases of eclampsia the kidneys were damaged, as evidenced by the large amount of albumin passed, and yet high readings were found in the urine. The *d* values for the serum were not worked out on these cases, but granted that there was an excess of ferment entering the blood, one might conclude that the ferment came through the kidneys with the albumin.

7. High readings in the urine were never found in pure cases of renal disease; they were either normal, subnormal, or zero.

8. Values up to 100 units were found in certain acute infective conditions without pronounced renal damage, but the only readings found above this mark were those in the urines from cases of pancreatic disease, certain forms of eclampsia, and one case of 'acidosis' in a child. The readings found in some of these cases were so high as to distinguish them from any other pathological condition examined.

9. All the cases of undoubted pancreatic disease, two being verified by operation and one by microscopical examination, gave high readings whether due to malignant or inflammatory processes. It is, therefore, likely that in certain forms of the toxaemia of pregnancy the pancreas is involved.

10. The test may, therefore, be a valuable help in the diagnosis of these conditions.

11. In diabetics on strict treatment subnormal readings were generally found, and large alterations in the total amount of urine or sugar passed per twenty-four hours had little or no effect on the *d* values. In severe cases the readings were lower than in the milder forms, although in view of the excessive dilution of the urine the total amount of ferment excreted was well within normal limits.

In conclusion my best thanks are due to Dr. L. S. Dudgeon for much valuable advice in my work, and I am most grateful to certain of the nursing staff of St. Thomas's Hospital and the General Lying-in Hospital, from which nearly all my cases were drawn, for the trouble and care taken in keeping the specimens for me.

REFERENCES.

1. v. Benczur, *Wien. klin. Woch.*, 1910, xxiii. 890.
2. Bial, *Inaug.-Dissert.*, Breslau, 1892.
3. Braunschweig, *Inaug.-Dissert.*, Leipzig, 1910.
4. Caspar and Richter, quoted by Wohlgemuth.
5. Clark, *Glasgow Med. Journ.*, 1905, lxiii. 416.
6. Cohnheim, *Virchow's Arch. für path. Anat. u. Physiol.*, xxviii. 241.
7. Cole, *Journ. Physiol.*, Camb., 1904, xxx. 202.
8. Delezenne and Pozerski, *Compt. rend. Soc. Biol.*, Paris, 1903, lv. 690.
9. Foster, M., *Journ. of Anat. and Physiol.*, Edin., 1867, i. 111.

10. Hanriot, *Compt. rend. Soc. Biol.*, Paris, 1896, xlviii. 925.
11. Hedin, *Journ. Physiol.*, Lond., 1904, xxx. 155.
12. Hirata, *Biochem. Zeit.*, Berlin, 1910, xxviii. 23.
13. Opie, *Johns Hopkins Hosp. Bull.*, 1902, xiii. 117.
14. Opie, *Diseases of the Pancreas*, Philad., 1903.
15. Röhmann, *Ber. d. deutsch. chem. Gesellsch.*, Berlin, 1892, xxv. 3654 and 1894, xxvii. 3251 ; *Archiv f. d. ges. Physiol.*, Bonn, 1892, lii. 157.
16. Robson and Cammidge, *The Pancreas: its Surgery and Path.*, Philad. and Lond., 1907.
17. Rosenthal, *Deutsche med. Woch.*, 1911, xxxvii. 1. 923.
18. Rosenthal, *Berl. klin. Woch.*, 1912, xlix. 1265.
19. Starling and Knowlton, *Journ. Physiol.*, Camb., 1912, xlv. 146.
20. Still, *Common Disorders and Diseases of Childhood*, Lond., 1909.
21. Wilenko, *Berl. klin. Woch.*, 1908, xlv. 1060.
22. Wohlgemuth and Noguchi, *ibid.*, 1912, xlix. 1069.
23. Wohlgemuth, *Biochem. Zeit.*, Berlin, 1908, ix. 1 and 1909, xxi. 381.
24. Wohlgemuth, *Berl. klin. Woch.*, 1910, xlvi. 1444.
25. Wohlgemuth, *Zeitschr. für Urologie*, Berlin u. Leipz., 1911, v. 801.
26. Wynhausen, *Berl. klin. Woch.*, 1910, xlvi. 2107.

Other References.

Gehrig, *Pflüger's Archiv f. die ges. Physiol.*, Bonn, xxxviii. 85.
Grutzner, *Bresl. Aerztl. Zeitschr.*, 1882, iv. 193.
Hoffmann, *Dissert.*, Tübingen, 1890.
Holovtschiner, *Virchow's Archiv f. path. Anat. u. Physiol.*, Berlin, 1886, civ. 42.
Lemaire, *ibid.*, 1903, lv. 1446.
Leo, *Verhandl. des Kongr. für inn. Medizin*, Wiesb., 1888, vii. 364.
Lepine, *Wien. med. Presse*, 1892, xxxiii. 1081.
Loeper and Ficaï, *Arch. Méd. Exp. et d'Anat. Path.*, Paris, 1907, xix. 722.
Marino, *Deutsch. Archiv f. klin. Med.*, 1911, ciii. 325.
Nigay, *ibid.*, 1908, lxiv. 793.
Pariset, *Compt. rend. Soc. Biol.*, Paris, 1904, lvi. 720.
Plósz and Tiegel, *Pflüger's Archiv f. die ges. Physiol.*, Bonn, 1873, vii. 391.

'OSLER'S SIGN' AND CERTAIN CUTANEOUS PHENOMENA SOMETIMES ASSOCIATED WITH HEART DISEASE

By F. PARKES WEBER

Apart from ordinary subcutaneous oedema in cases of general dropsy from failure in the mechanism for the circulation of blood there are a few phenomena to be observed in the skin and subcutaneous tissue which are occasionally more or less dependent on some form of cardiac disease. One of these should be mentioned before the others, inasmuch as it is, as far as I know, only met with in heart disease and is of real diagnostic importance, since it almost certainly indicates not only the presence of heart disease, but the nature of the heart disease from which the patient is suffering.[1]

Osler's Sign of Chronic or Subacute Malignant Endocarditis.

In certain cases of chronic or subacute malignant endocarditis (endocarditis maligna lenta) minute circumscribed painful erythematous swellings appear in the skin and subcutaneous tissue, especially of the hands and feet. They are intensely tender to pressure and disappear gradually in from three or four days to a week or more. Each one of the spots or little 'lumps' is apparently due to a localized acute inflammatory exudation around a blood capillary, or possibly (in the case of the slightly larger and deeper subcutaneous 'lumps') arteriole, which has suddenly become plugged by a minute infective embolus from a vegetation in a heart affected with endocarditis maligna lenta. In such cases the infective agent (whatever microbe it may be), though pyogenic in nature, seems unable to excite actual suppuration in any (or in most) of the embolic infarctions which result in the skin or elsewhere (lungs, brain, spleen, kidneys). This failure to produce suppuration may depend on low virulence of the microbic parasites or on the nature of the resistance in the blood and tissues of the host. The minute cutaneous foci in question may possibly sometimes be due, not to an actual embolus from a cardiac vegetation, but to the local lodgement of microbes circulating in the blood ('bacteriaemia' in cases of malignant endocarditis), setting up a circumscribed acute inflammation about the wall of the capillary or

[1] As will be seen later, I do not mean that the heart disease in question (chronic or subacute malignant endocarditis) is always due to the same species of microbic parasite.

[Q. J. M., April, 1913.]

arteriole on which the microbes have lodged. I am not aware that any of the little painful lumps have ever been satisfactorily examined with the microscope, though I know of one having been excised during life in the hope of obtaining by means of it an autogenic vaccine which could be used for treatment.

Osler's spots vary considerably in size—from about the size of a pin's head to that of a small pea—and may or may not be raised above the general level of the skin. They also vary in colour. These differences seem to me to depend on the intensity and stage of the local inflammatory process and the depth of the focus below the surface of the skin. The smaller and redder of the spots, which are, I think, generally seen on the fingers, probably arise when the inflammatory focus is very superficial, whereas the larger and less-highly coloured 'tender lumps' (up to the size of a small pea) occur when the inflammatory focus is rather more deeply seated, and are more decidedly felt as distinct nodules in and under the skin. The larger ones last a few days longer than the smaller ones; I have felt them in the palm of each hand, whereas the smaller ones, as I have already stated, are more likely to be met with on the fingers (or toes). The smallest ones may appear as punctiform erythematous spots on the tips of the fingers; for instance, in the cushions on the flexor aspects of the terminal phalanges. When they first appear they are tender and associated with slight diffuse redness and swelling, but in two or three days the pain, together with the surrounding flush and swelling, passes off, leaving a small erythematous point behind, which is not necessarily raised above the general level of the skin about it.

I have here used the short terms, 'Osler's spots' and 'Osler's symptom', because, although I am not sure who first described the spots in question, it was, as far as I know, Sir William Osler (3) who first called general medical attention to their full diagnostic importance and distinguished them from the ordinary purpuric eruptions not rarely met with in cases of malignant endocarditis. Indeed, there are cases of chronic malignant endocarditis which may clinically be termed 'ambulatory' cases, because the patients can often get about and even do work; they may occasionally lose their fever for a time, or may get physically accustomed to their fever, which they may ascribe to mild malaria, &c. Such persons may have the physical signs of old rheumatic or of congenital cardiac valvular disease, but the presence of superadded chronic malignant endocarditis is sometimes not recognized by the medical men who examine them. Slight enlargement of the spleen (septic, or due to embolic infarcts) is a most important sign when present, but a history of old malarial splenomegaly may lead to confusion. Albuminuria and haematuria due to septic nephritis or renal emboli, if present, may facilitate the diagnosis, but Osler's spots, when they occur, are of invaluable diagnostic importance. I do not go quite so far as to say that they will never be found in any cases save cases of malignant endocarditis, though I have as yet not observed them or heard of their occurrence in any other cases. They might conceivably occur in the excessively rare cases of malignant endarteritis of the aorta or pulmonary artery, which are doubtless of the same infective nature as malignant endocarditis. In one such case, described by

Dr. Karl Fürth and myself in 1905 (1), none of the cardiac valves were found diseased after death, but on the anterior wall of the pulmonary artery, about ¾ inch distal to the pulmonary valve, was a rough warty outgrowth, projecting on the inner surface of the vessel.

I give the following as specimens of the class of cases in which Osler's spots occur:

Case I. A man, aged 25 years, under my care at the German Hospital in 1909. History of rheumatism in childhood. Recently he had been operated upon at another hospital, apparently for supposed appendicitis, but the fever continued after the operation. At the German Hospital he had pyrexia of a septic type, the physical signs of cardiac valvular disease, retinal haemorrhages, enlargement of the spleen, and an attack of pain in the region of the spleen (possibly due to embolism). Minute red spots were observed to occur on the fingers, &c.

Case II. A German waiter in London, aged 24 years, under my care at the German Hospital in 1910, with the physical signs of aortic valve incompetence, and obviously suffering from chronic malignant endocarditis. In April, 1910, a few Osler's spots were observed, one on the outer side of the right foot near the little toe, two on the terminal segments of fingers. The two last mentioned were punctiform purpuric spots not raised above the general surface of the cushions of the finger-tips; they were at first tender to pressure and associated with slight diffuse redness and swelling. Apparently the pain and surrounding redness and swelling passed off in a few days, leaving a small purpuric or erythematous point behind them. This patient died in June, 1910, the temperature having been subnormal for the last six days of life. The *necropsy* showed warty vegetations on the aortic and mitral valves; the aortic curtains showed also unusually remarkable congenital 'fenestration'. Vegetations were likewise present on the chordae tendineae, and on the endocardium in the neighbourhood of the aortic and mitral valves. There was pericarditis with serous pericardial effusion. The spleen was enlarged and showed non-suppurating embolic infarcts of various dates. There were haemorrhages in the kidneys, and these organs were large and pale (the urine had sometimes contained blood during life).

Case III. A married woman, aged 30 years, with signs of chronic malignant endocarditis. The fatal illness lasted apparently from May to September, 1912, but she was under my care only for part of that time. She had the physical signs of incompetence of the aortic valve, irregular fever, and enlargement of the spleen. An attempt to obtain an autogenous vaccine from the patient's blood for therapeutic purposes failed. The cultures from the specimen of blood were reported to show only Staphylococcus albus—probably as an impurity. In regard to Osler's symptom there were minute red tender spots on the hands lasting three days or so, but tender spots were also observed on the palms, attaining the size of a small pea, which disappeared after a week or so.

Chronic Purpura in Chronic Malignant Endocarditis.

Slight purpura is not very rarely met with in patients with various chronic diseases. It may occur in patients with chronic cardiac insufficiency, and it may likewise occur in patients with chronic renal or hepatic insufficiency (in chronic nephritis and in late hepatic cirrhosis). In such chronic cases where

there is a condition of general malnutrition, the taking of iodide of potassium may temporarily induce purpura, notably purpura of the so-called 'orthostatic variety', that is to say, when the position of the purpuric spots is chiefly on the dependent parts of the body, especially on the legs when the patients first get up after having been kept for a long time lying in bed. Purpura appearing in the final stages of chronic cardiac failure is probably not only associated with general malnutrition, but also frequently due to 'terminal' infections.

The purpura often observed in cases of malignant endocarditis is doubtless of septic origin and connected with the toxaemic (and probably sometimes the actually 'bacteriaemic') condition of the blood; the purpuric spots on the skin in such cases are often associated with haemorrhages in the retinae, and at post-mortem examinations little haemorrhages in or beneath the mucous and serous membranes are usually also found, as they are indeed at necropsies on cases of septic infections of all kinds. As a striking example of chronic purpura in chronic malignant endocarditis I shall shortly describe the following case:

The patient was a sailor, aged 28 years, who was under my care at the German Hospital in 1909. His illness was said to have commenced about two years previously, when purpuric spots appeared on both legs. Since then he had gradually become weaker and paler and had noticed an increasing swelling (enlarged spleen) in the left side of his abdomen. He had been treated at several London hospitals, where apparently the diagnosis of splenic anaemia was made. He was extremely pale, weak and wasted; examination of the blood showed anaemia with leucopenia, the spleen and liver were both enlarged, and there was a systolic apical murmur over the heart, which was somewhat hypertrophied. There was a little fever. A remarkable feature of the case was the appearance of the skin of the lower extremities. Both legs below the knees, and the lower inner aspects of the thighs, were covered with spots of brown pigment. This remarkable brown pigmentation was evidently the result of repeated spots of haemorrhage into the skin, for amongst the pigment spots were some fresh red petechiae. On the arms and trunk there were likewise a few purpuric spots. There was a tendency to bleed from the gums, and a few conjunctival petechiae were noticed. Ophthalmoscopic examination showed the presence of retinal haemorrhages also. During about the last three weeks of life there was seldom any fever. At the *necropsy* the heart was found much enlarged, there was old thickening (probably rheumatic) of the mitral valve, with a soft organized thrombus attached to one part of it. In the left auricle, and attached by its pedicle to the interventricular septum, was a large polypoid excrescence, evidently an old organized thrombus, the free end of which was opaque, hard, and partially calcified. The spleen and right kidney showed non-suppurative embolic infarctions (4).

Acrocyanosis and Livedo Reticulata (Livedo Annularis) in Chronic Cardiac Failure.

Acrocyanosis and livedo reticulata are certainly not usually in any way connected with heart disease, but doubtless they may be aggravated by chronic cardiac insufficiency, and so also may perhaps attacks of Raynaud's symptoms. Of the latter I have seen a mild example ('local syncope' of the fingers) in a middle-aged woman, the subject of old cardiac valvular disease. Another woman, aged 54 years, whose case I have recorded elsewhere (5), has mitral stenosis from a severe attack of rheumatic fever at 19 years of age, and she has for a long time been subject to Raynaud's phenomena (of the 'local asphyxia' type) in the feet and hands. She likewise has a striking condition of livedo reticulata, which she thinks developed after the rheumatic fever; it is best marked in the skin of the extensor surfaces of the upper extremities, but is well marked also over the lower part of the thighs (near the patellae) and over the whole of the back. In that case there is some evidence of arteriosclerosis and previous syphilis, though the Wassermann's reaction for syphilis is at present negative. A younger woman, aged 29 years, under my care in April, 1910, with cardiac and renal disease, had a peculiar condition of livedo reticulata over the back of each hand and the adjacent part of each forearm, which I at first took to be a kind of 'erythema figuratum ab igne' from warming her hands in front of the fire. This was, however, not the case, and the localized livedo in question had apparently been present from early life, and therefore also almost certainly had no connexion with the cardiac and renal disease. I have since seen the same kind of permanent livedo reticulata in a young woman, localized to the ulnar side of the dorsal aspect of both hands. I am inclined to think that such symmetrical patches of permanent livedo reticulata often, but certainly not always, have a congenital or developmental origin analogous to that of the groups of cutaneous branching hair-like telangiectases met with in some young persons.

In another case, however, the matter was somewhat different. The patient, a young woman, aged 20 years, was in 1912 under the care of my colleague, Dr. Karl Fürth, who has kindly allowed me to refer to it. She had a grave form of mitral stenosis[2] with cardiac insufficiency. There was well-marked livedo reticulata of both the upper and lower extremities, on the extensor surfaces and especially about the knees. The front of the thorax about the breasts showed livedo reticulata also, but to a lesser degree. Her lips and tongue were cyanosed, and her face arrested attention owing to each cheek appearing as a large bluish-red blotch of colour. There was evidently great general congestion of capillaries, and examination of her blood showed moderate polycythaemia (6,340,000 red cells to the cubic millimetre of blood). Apparently

[2] A subsequent post-mortem examination showed tough ring-like mitral stenosis, nutmeggy liver, &c.

the patient had had rheumatic fever three years previously, and the livedo reticulata had developed since then. She had not aided its development (as in cases of 'erythema figuratum ab igne') by sitting in front of a fire. In this case I think it quite possible that the extreme capillary engorgement, as shown by the high colour of the cheeks and the cyanosis of the lips and tongue, favoured the occurrence of the livedo reticulata, but even here it should be observed that the affected areas of skin were more or less those selected by livedo reticulata of unknown aetiology (including congenital and early development cases); for instance, the extensor surfaces of the legs about the knees.

The localization alone is sufficient to distinguish the reticular livedo in these cases from the reticular 'erythema ab igne' ('erythema figuratum ab igne') over the shins, due to sitting in front of a fire, and from the similar reticular 'erythema a calore' due to the prolonged or habitual application of hot fomentations or india-rubber hot-water bottles (on account of pain, &c.) to the back or to the abdomen.

Chronic venous obstruction of any kind may favour or cause the appearance of a local livedo reticulata. Thus, chronic obstruction from any cause in the great veins leading from the upper extremities may be associated with reticular livedo and reticular pigmentation in the forearms.

The extreme capillary engorgement in one of the cases I have mentioned (the young woman aged 20 years) reminds me somewhat of the appearance I saw in the viscera at the post-mortem examination on a young man with old rheumatic mitral stenosis and chronic cardiac failure. The omentum and appendices epiploicae were transformed into red highly vascular structures not at all resembling ordinary fat. Microscopical examination, however, showed that the red colour was due merely to intense engorgement of the capillaries with blood. F. Lommel perhaps alluded to a similar condition when, in describing what was found at the necropsy of a case of chronic stenosis of the portal vein with final complete thrombosis (2), he wrote: 'The tremendous congestion in the territory of the portal vein manifested itself not only in the extreme engorgement of all the abdominal organs with blood, but also in the development of numerous *angiomata*[3] (in connexion with the abdominal organs) distended with blood.'

'Terminal' Cutaneous Complications in Cases of Chronic Cardiac Failure.

I will here merely mention the purpuric and erythematous manifestations, which are doubtless often associated with 'terminal' infections. In the recent case of a man, aged 24 years, with oedema and ascites from chronic cardiac failure (old rheumatic mitral stenosis), I observed during the last three or four

[3] I suppose that very vascular connective-tissue structures *resembling angiomata* are meant.

days of life a bright red erythema, chiefly affecting the hands and feet. There was evidently considerable intestinal catarrh, and it is possible that the cutaneous erythema was due to toxins absorbed from the bowel. In terminal stages of cardiac failure, as in other terminal cases, an acrosphacelismus occasionally occurs, and I think I have seen gangrene of the tip of the nose in one such patient. Gangrene of this kind must not be confused with the occasional gangrene of extremities due to arterial embolism in heart diseases.

REFERENCES.

1. Fürth, K., and Weber, F. Parkes, *Edin. Med. Journ.*, 1905, New Series, xviii. 33–38.
2. Lommel, F., *Münch. med. Woch.*, 1908, lv. 275.
3. See especially his account of 'Chronic Infectious Endocarditis' at the Meeting of the Association of Physicians of Great Britain and Ireland, June 12, 1908 (*Quarterly Journal of Medicine*, Oxford, 1909, ii. 219).
4. Weber, F. P., *Trans. Med. Soc.*, London, 1910, xxxiii. 83.
5. Weber, F. P., *Brit. Journ. Dermat.*, Lond., 1913, xxv. 81.

NOTES ON FOUR CASES OF FULMINATING PNEUMONIA FROM A PUBLIC INSTITUTION

By ERNEST GLYNN

From the Thompson Yates Laboratories, University of Liverpool

With Plate 18

Epidemics of pneumonia in industrial schools are not very uncommon, and have recently attracted some attention.

J. P. McGowan and Charles McNeil (4) have collected from an industrial school near Edinburgh a large number of cases which occurred during the last twelve years. They included 'three fairly distinct clinical types': (*a*) 'Twenty cases with a very rapidly fatal issue; in one or two the boys going to bed well and being found dead in bed next morning'; (*b*) 'fifty-one cases of pneumonia, peculiar in the absence, paucity, or irregularity of the physical signs of consolidation'; (*c*) '175 cases of high fever and acute general symptoms of short duration. The simultaneous occurrence of the three types and the similarity of the general symptoms in all the groups pointed to their being differing forms of one disease.'

'The common clinical manifestations were the very sudden onset of high fever, with headache and vomiting, cough, and loose blood-stained sputum; labial herpes; and symptoms of severe poisoning of the central nervous system, stupor, coma, &c.

'The suggestion of irregular pneumonia was borne out by the condition of the lungs at autopsy, which showed either acute general congestion, or an irregular, often small area of consolidation. When sought for pneumococci were obtained from the lung, and in one case from the blood in other organs. No other organisms were cultivated in the lungs or other tissues.'

Unfortunately, it is not stated how many autopsies were made, or how often and by what method the pneumococci were demonstrated.

Charles Macalister (3) described four cases of death occurring in a few hours among the boys of an industrial school, which he attributed to pneumonia; one is summarized below.

In July, 1897, a healthy boy complained of headache at 8 p.m. He got out of bed early next morning, but was too weak to return. His breathing was

difficult. He soon became cyanosed and unconscious. The temperature rose to 101·6° and death took place at 8 a.m., twelve hours after the onset of illness.

Gastro-intestinal symptoms were a prominent feature in two of the other cases.

Cases of Pneumonia in a Public Institution.

Two small epidemics of pneumococcal infection of the lungs occurring in another Liverpool public institution have come under my notice. There have been fifteen cases with four deaths. The disease in these four ran a most unusual course. Two terminated fatally in about seven hours after the onset of the first symptom, and the ordinary post-mortem signs of pneumonia were completely absent. Two only survived about thirty hours; in one there was definite pneumonic consolidation, in the other consolidation had begun. As the disease in all four cases developed with 'sudden severity', they have been described as 'fulminating' (Gould (2)). The first epidemic lasted from October, 1909, to March, 1910; there were eleven cases with three deaths; seven of the cases were mild. The second epidemic began in October, 1912; three cases have occurred with one death. I am much indebted to Dr. McFeely, physician to the institution, and to the matron for very kindly furnishing me with clinical particulars.

Fulminating Pneumonia without Consolidation.

Case I. March, 1910, McC., aged 15. Was working on March 1 from 7 a.m. to 8 a.m. After breakfast, at 9.30 a.m., the Governor noticed him looking blue and cold, but he stated, 'I feel all right, sir.' He was, however, sent to the kitchen fire to warm himself. At 11 a.m. he still maintained he was quite well, but at 2 p.m. complained of headache, vomited, and was sent to bed; the temperature was 102°. Later he became delirious, comatose, and died at 4 p.m., 6½ hours after he was first noticed to be ill.

A post-mortem was performed by me at 4 p.m. next day in the institution. The body was that of a well-nourished boy. A thorough examination was made of all the organs, including the brain, spinal cord, stomach, intestines, adrenals, &c. Nothing abnormal was detected, except slight congestion of the brain, redness and enlargement of the bronchial lymphatic glands, injection of the trachea, which contained some frothy blood-stained mucus, also a moderate amount of oedema and congestion of the lungs. There was no trace of consolidation in the lungs either to the naked eye or on palpation. The pleura contained a few petechial haemorrhages.

Bacteriological Examination. Specimens of the cerebro-spinal fluid and heart blood were examined microscopically without result.

The dramatic nature of the illness and the enlargement of the bronchial glands suggested the possibility of pneumonic plague. Smears were therefore made from the lung juice and examined microscopically. They swarmed with Gram-positive capsulated diplococci resembling pneumococci.

A mouse was injected with the blood from the lung and died two days later from typical pneumococcal septicaemia.

The microscopical appearances of the lung and kidneys will be referred to later.

Case II. November, 1912, T. W., aged 15. Played football on November 15, complained next day of a kick on leg received during the game. He was confined to bed, a fomentation applied, and at midday was seen by Dr. McFeely, who found nothing wrong. Shortly afterwards he complained of headache; at 2 p.m. vomited greenish yellow material, and the temperature rose to 104°; later he had convulsions, became comatose, the temperature reaching 106°. He died at 7 p.m., about seven hours after the acute symptoms developed.

The post-mortem was made in the Home twenty-one hours after death. There was a slight bruise on the leg. The appearance of the lungs and other organs was exactly similar to that found in the first case. I found no trace of pulmonary hepatization.

Bacteriological Examination. Stained preparations of the heart blood showed no bacteria after prolonged examination, but the lung juice was swarming with Gram-positive capsulated diplococci resembling pneumococci, occurring singly and in clusters. A mouse was injected with the blood from the heart and another with lung juice. The latter died from typical pneumococcal septicaemia, but the former survived.

Cultures were made from the cerebro-spinal fluid, the heart blood, and lung juice. From the cerebro-spinal fluid there grew a few colonies of Staphylococcus albus; from the heart blood, pneumococci, a few colonies of Staphylococcus albus, and of a Gram-negative bacillus; from the lung juice, pneumococci, a few colonies of the Gram-negative bacillus, and of a Gram-positive bacillus.

The reactions of the Gram-negative bacillus were as follows: Glucose broth, acid and gas; cane sugar, lactose, and dulcite broth, no change; litmus milk, alkaline; gelatin, not liquefied.

The Gram-positive bacillus was of a diphtheroid type so frequently found on the skin or external mucous membranes.

Microscopic Examination of Cases I and II.

The microscopical appearances of the lungs and kidneys were almost identical in both cases, and may be summarized as follows:

Lungs. 1. Intense congestion (Fig. 2).

2. Though most of the alveoli were normal there were a certain number of irregular airless patches scattered here and there (Fig. 1) due to—

A. Collapse of small groups of alveoli.

B. An exudate of serous fluid or erythrocytes, in some places combined with a few 'catarrhal' cells, and occasionally, though very rarely, polymorphonuclear leucocytes (Fig. 3). Fibrin was absent.

3. The epithelium of many bronchi was desquamating and blood was present in the lumen of one (Fig. 4).

4. The pleura, apart from congestion of the sub-pleural vessels, was normal.

5. Red thrombi, some containing several leucocytes, were present in many of the blood-vessels. This was indicated by the yellow brown tinge of the erythrocytes, their failure to stain red with eosin, and by the amorphous brown haematoidin pigment in the polymorphonuclear leucocytes (Fig. 5). The appearances were very similar to some met with in primary thrombosis of the pulmonary artery (Glynn and Knowles). There was also a considerable amount of brown pigment—quite distinct from the black carbon pigment in the catarrhal cells, the alveolar walls, and even in many of the polymorphonuclear leucocytes situated in blood-vessels which showed no microscopical evidence of thrombosis.

The 'haemosiderin reaction' was not obtained, but this reaction is also very frequently absent in the pigmented thrombi of pulmonary thrombosis.

6. Gram-positive diplococci, morphologically resembling pneumococci, were scattered irregularly through the lung in clusters sometimes of enormous numbers. The pneumococci were never deposited in the capillaries or blood-vessels as so frequently obtains in septicaemia, but were confined to the walls of the bronchi and lumina and alveoli (Figs. 6 and 7, also 12).

No *other* bacteria were seen in specimens stained with Gram or methylene blue except one or two bacilli in the lungs of Case II.

Kidneys. 1. Congestion of the glomerular vessels and of the vasa recta, &c. (Fig. 11).

2. Profound parenchymatous degeneration of groups of secreting tubules, many of the nuclei having totally disappeared, and desquamation of the epithelium in the smaller cortical collecting tubules.

3. A few red thrombi similar to those met with in the lungs were also present in the smaller vessels. The amount of blood pigment was considerable; it was deposited in the walls of the glomeruli, the epithelium of the tubules, and also in many of the leucocytes present in the blood-vessels, some of which showed no evidence of thrombosis. In Case II the pigment granules in the tubules were smaller and more diffusely dusted all over the tissues than in Case I (Figs. 10 and 12, also 6).

Brain. Case II. A section of the cerebral cortex showed a very few red thrombi in the smaller vessels, and rarely a pigmented leucocyte in other vessels in which thrombosis had apparently not occurred. No pneumococci or other bacteria were demonstrated in the sections.

Comments on Cases I and II.

The evidence that death in both cases was due to a pure infection with Fränkel's pneumococcus is, first, the presence of enormous numbers of Gram-positive organisms, morphologically resembling pneumococci in the smears from the lung juice, and in the microscopical sections of the lungs combined with the absence of other bacteria; second, the production of typical pneumococcal septicaemia in the inoculated mice.

Cultures were only made from Case II, where, in addition to pneumococci, a few colonies of Staphylococcus albus and of two non-pathogenic bacilli were cultivated. These organisms were due to post-mortem invasion or possibly contamination.

In both cases the infection with pneumococci was primarily a pulmonary one, and had hardly reached the stage of a septicaemia for the following reasons: the failure to find pneumococci in the smears of the heart blood, and to produce pneumococcal septicaemia in the mouse injected wtth the heart blood of Case II, and the absence of pneumococci in the microscopical sections of the kidneys or cerebral cortex (Case II), also in the blood-vessels in the lungs, and, lastly, the limiting of the pneumococci to the walls and lumina of the bronchi and alveoli.

The pneumococci evidently liberated most powerful toxins, as indicated by the profound degeneration in the kidneys, and the extensive thrombosis and haemolysis leading to the deposition of blood pigment not only in the tissues of

the lung and kidneys, but even in the circulating leucocytes. These facts partly explain the rapidity with which death occurred.

The pneumococcus does not usually haemolyse blood in cultures. It is unfortunate that the microscopical sections of the tissues were not examined and the thrombosis and haemolysis recognized until the pneumococci had been destroyed, consequently there was no possibility of testing the biological properties of these particular strains experimentally either *in vivo* or *in vitro*.

Fulminating Pneumonia with Consolidation.

Case III. This occurred in October, 1909, and was the initial one of the epidemic.

T. W., aged 13. Was at work all morning on October 18. After midday dinner he was attacked with vomiting, headache, and rigors. A provisional diagnosis of cerebro-spinal meningitis was made, and he was removed at 8 a.m., October 19, to the City Hospital, Fazakerley, under the care of Dr. Rundle, to whom I am indebted for further particulars.

On examination, patient was cyanosed and comatose, temperature 99·2°, pulse 124, respirations 48. There was 'tubular breathing, crepitations, and dullness on percussion, over a considerable patch in the right infra-scapular and scapular regions'. The alimentary, circulatory, and nervous systems were normal. Death took place at 8.30 p.m., about thirty hours after the onset of the disease.

Post-mortem. The lungs only were examined at the post-mortem. 'There was engorgement of the right upper and middle lobes, most marked in the latter; the lung tissue was crepitant, and floated in water. The bases of both lungs were oedematous. The bronchi contained blood-stained frothy mucus; there were no naked-eye changes in the bronchial glands.'

Bacteriological Examination. 'Pneumococci were very abundant in films from the affected lung and bronchial secretions.'

It is very probable that consolidation had begun in part of the right lung on account of the 'dullness and tubular breathing'. Partial consolidation is consistent with the lung still 'floating in water'.

Case IV. January 11, 1910. T. G., aged 15. Previous health good. Illness began on the morning of January 11 with severe headache and vomiting. He was admitted into Dr. Abram's ward at the Royal Infirmary at 1.30 a.m., January 12, in a semi-comatose and delirious condition—temperature 101·6°, respirations 33, pulse imperceptible—and died at midday, about thirty hours after the onset of illness. The results of a blood-count were—'Leucocytes, 23,000 per cm.; polymorphs, 90·5 per cent.; small lymphocytes, 7 per cent.; large lymphocytes, 2·5 per cent.; eosinophils, none seen.'

The post-mortem, which I performed twenty-six hours after death, is summarized below:

Brain, 49 oz., normal, no excess of cerebro-spinal fluid. Thymus persistent, weight 2 oz.; measures in the middle line from above downwards 2 in., the right lobe 3½ in. Trachea: mucous membrane intensely injected, lymphatic glands in the neighbourhood twice normal size. Pleura: a few sub-pleural petechial haemorrhages specially marked at the base. No pleurisy. Lungs: right normal, left upper lobe normal; posterior surface of lower lobe contains a patch of fused lobular (pseudo-lobar) pneumonia extending from the apex to the base, the width irregular, averaging about 2 in.; the hepatized area was bright red and sank in water. Heart, 11 oz. Both ventricles contained yellow 'agony' clots. Stomach, large and small intestines, normal. Liver, 51 oz., some congestion. Spleen, 6 oz., firm. Kidneys, 5 oz., somewhat cyanosed.

Bacteriological Examination. A mouse inoculated subcutaneously with some of the material from the hepatized portion of the left lung died in three days. Typical Gram-positive capsulated pneumococci were present in its blood.

Microscopical examination of the affected lung showed intense congestion. Blood pigment was scanty; it was present in some of the alveolar walls, and in certain groups of the leucocytes in the exudate, but very rarely in the leucocytes in the blood-vessels, and partial or complete filling of the alveoli with polymorphonuclear leucocytes; erythrocytes and fibrin were occasionally present.

Cases terminating in Recovery.

Three out of the eleven cases which recovered were treated in a hospital, and may be briefly alluded to.

Case V. 1910, C. M., aged 11. Was suddenly taken ill on March 28 with vomiting and headache.

The symptoms at first pointed to a bilious attack, but Dr. McFeely diagnosed pneumonia, and the patient was admitted into Dr. Buchanan's ward at the Royal Infirmary on March 30.

There were several patches of consolidation in the right lung and one in the left. Temperature fell by lysis. The sputum contained pneumococci and the patient was treated with pneumococcal vaccine.

Case VI. December 10, 1912, E. T., aged 14. The illness began with vomiting. He was admitted to the Royal Southern Hospital, under the care of Dr. Macalister, with a temperature of 101°, respirations 28, cough and mucopurulent sputum. The chest was full of coarse bubbling râles, but no marked dullness appeared. His temperature was intermittent for six days. Smears of the sputum revealed large numbers of pneumococci, and Dr. Alexander, the Pathologist, confirmed this by inoculating a mouse.

Case VII. December 20, 1912, E. C., aged 15. The illness began with vomiting and pain in the right side. He was admitted to the Royal Southern Hospital with a temperature of 101°, respirations 30, and bubbling râles all over the chest, but no definite dullness. Intermittent pyrexia continued for a week. The sputum also contained numerous pneumococci, confirmed by inoculation into a mouse.

The eight other cases were of a mild type, and Dr. McFeely treated them in the school. They all developed between January 13 and 30, 1910, very shortly after removal of T. G., Case IV, who died in the Royal Infirmary.

Etiology.

There is no evidence to determine whether the 'seed' or the 'soil' or both are responsible for the atypical nature of these infections. Fulminating or 'malignant' cases may occur in other infective diseases, as plague, cholera, scarlet fever, and measles. It may be due to some modification in the biological characters of the pneumococci; this is suggested by the extensive deposition of blood pigment in the tissues, and the very profound degeneration of the kidneys. It may be due to some unusual diathesis in the patient, acquired perhaps from the school environment. The school was in a good sanitary condition, and, like other similar institutions, is under Government supervision.

McGowan and McNeil suggest that the deviation from the ordinary type of pneumonia is 'explained by the existence of a morbid diathesis, which in the fatal cases conforms to the classical descriptions of the morbid anatomy of status lymphaticus, with the addition of extreme hyperplasia of the thyroid gland'.

In this connexion it is noteworthy that in one of the four fatal cases the thymus was much enlarged and weighed 2 oz. The thyroid was not examined microscopically in any case. There is much need of further research on the whole question.

Summary and Conclusions.

1. Fifteen cases of atypical pneumonia occurred during two mild epidemics in a Liverpool public institution; in seven the pneumococci were looked for and demonstrated.

2. The four fatal cases were of a fulminating type, two deaths occurring about seven hours, and two about thirty hours after the first symptom.

3. *The two boys dying in about seven hours showed, apart from congestion, no macroscopic, and so little microscopic evidence of pneumonia, that but for the demonstration of the pneumococci in the lung alveoli, the cause of death would not have been discovered.*

4. In both the infection was primarily a respiratory one, involving the lung tissue, and had hardly developed into a pneumococcal 'septicaemia'.

5. In both the organisms had produced profound degeneration of the kidneys, thrombosis and haemolysis in the vessels of the lung and kidney, and the deposition of blood pigment not only in the lung and kidney tissue and in the thrombi, but also in some of the leucocytes in vessels in which thrombosis had apparently not occurred.

6. In the two boys dying after about thirty hours' illness, consolidation was evidently beginning in the lungs of one, while those of the other contained a small patch of pseudo-lobar pneumonia. Pneumococci were demonstrated in both instances.

7. Clinically all the cases were rather atypical on account of the prominence of gastro-intestinal or cerebral symptoms, and the small amount or absence of consolidation.

8. There is not sufficient evidence to determine whether the atypical nature of the infections was due to some unusual character of the pneumococci as suggested by the thrombotic and haemolytic effects which occurred in two cases; or to some predisposition on the part of the patient, perhaps of the nature of status lymphaticus.

I am indebted to Dr. Moore Alexander, Dr. Abram, Dr. Buchanan, Dr. McFeely, Dr. Macalister, and Dr. Rundle for the information they have kindly supplied to me regarding the cases.

REFERENCES.

1. Glynn, E., and Knowles, R. E., *Brit. Med. Journ.*, 1910, ii. 1412.
2. Gould, *Medical Dictionary*, London (Lewis), 1909.
3. Macalister, C., *Brit. Journ.*, Child. Dis., 1905, ii. 105.
4. McGowan, J. P., and McNeil, Charles, *Proc. Path. Soc.*, Great Brit.; *Journ. Path. and Bacteriol.*, Camb., 1913, xvii. 412.

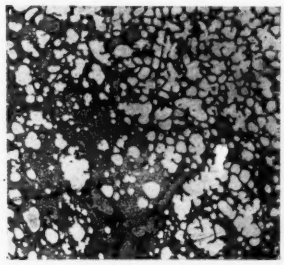


Fig.1. Case2. x15-Lung with airless patches from congestion, collapse and slight exudate.

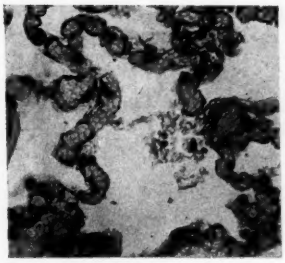


Fig.2. Case1. x300-Lung with congestion.

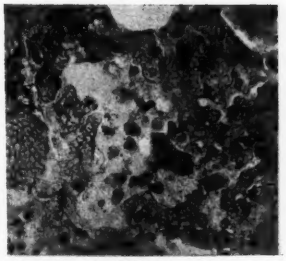


Fig.3. Case2. x300-Lung with congestion and slight exudate of "catarrhal" cells containing blood pigment.

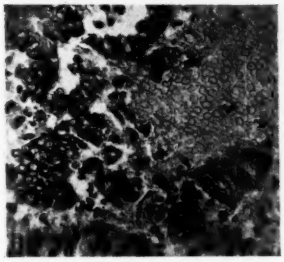


Fig.4. Case1. x300-Bronchus with desquamating epithelium and blood in lumen.

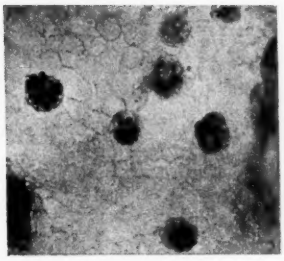


Fig.5. Case2. x1000-Blood in pulmonary vessel, the leucocytes contained blood pigment.

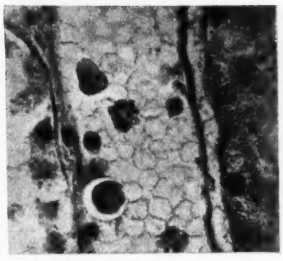


Fig.6. Case2. x1000-Blood in renal capillary, the leucocytes contain blood pigment; also two degenerated pigmented epithelial tubules.

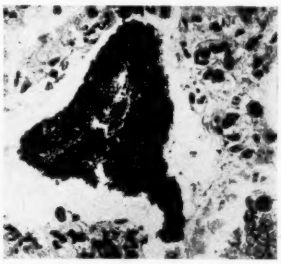


Fig.7. Case1. x750- Mass of pneumococci in lung alveolus. (Gram's stain)

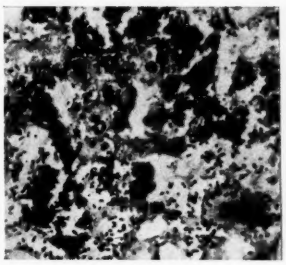


Fig.8. Case2. x1400-Mass of pneumococci and a few cells in lung alveolus. (Gram's stain)

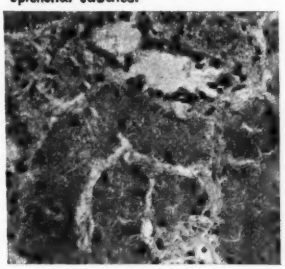


Fig.9. Case1x200-Kidney with degenerated and pigmented tubules.

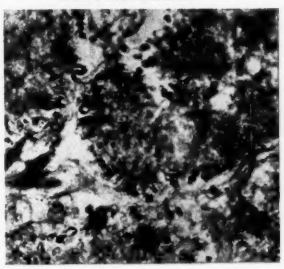


Fig.10. Case1. x1000-Kidney with degenerated and pigmented secreting tubules. All nuclei in the epithelial cells have disappeared except one.

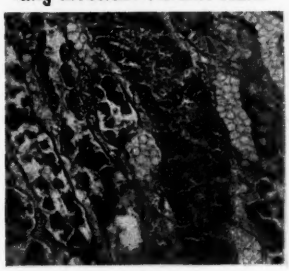


Fig.11. Case2. x200-Kidney with congestion, degenerated secreting tubules & desquamating collecting tubules.

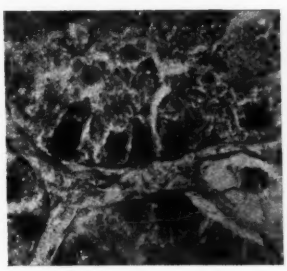


Fig.12. Case2. x1000-Kidney with degenerated and pigmented tubules. Pigmented leucocytes in capillary at right hand lower corner.

CRITICAL REVIEW

HAEMOLYSIS IN ITS CLINICAL ASPECTS

By CARL H. BROWNING

THE phenomenon of *haemolysis* or the laking of blood has been utilized in various ways for purposes of clinical investigation. Thus, many substances possess the property of laking human red blood corpuscles in the test-tube, and alterations in the resistance of the red cells to haemolytic agents have been found to be characteristic of certain diseases. On the other hand, human blood-serum, in virtue of containing one or both of the components—immune body and complement—which constitute a complex serum-haemolysin, exerts haemolytic action on the blood corpuscles of other species or other human beings and rarely on the individual's own corpuscles. Characteristic alterations in the content of the serum in these constituents have been observed at different ages and in various diseases, and their bearing on the question of resistance to disease in general has been much discussed. Further, an abnormal content of other body-fluids in haemolysins has been found, e.g. the presence of haemolysin in the cerebro-spinal fluid in meningitis and general paralysis. Serum also exerts a retarding or accelerating action on various other haemolytic bodies, and these effects have been widely investigated in a variety of conditions, with the result that certain changes have been found to occur with comparative constancy, although their significance is still not clear, e.g. the auxiliary action of the serum on cobra-venom haemolysis in cases of pregnancy and of malignant tumour. Again, infective agents produce modifications in the tissue-metabolism which are manifested by the appearance of 'antibodies' in the serum. These antibodies are specific for the particular infective agent involved, and they can frequently be detected by the fact that the patient's serum, in combination with the micro-organism concerned, possesses the property of inhibiting the action *in vitro* of a serum haemolysin (complement-deviation). Accordingly, the occurrence of the reaction of complement-deviation affords very important evidence of the aetiological relationship of a given micro-organism to a particular disease. The biological syphilis reaction of Wassermann, Neisser, and Bruck was discovered on this analogy, although it probably depends on a phenomenon of a different nature. In paroxysmal haemoglobinuria it has been shown that a haemolysin for the patient's red blood corpuscles is present in his serum, and there is good reason to suppose that the disease is caused by its action. Certain other

diseases, such as blackwater fever and some forms of anaemia, e. g. pernicious anaemia, are characterized by the occurrence of lysaemia; an investigation into the character and mode of action of the haemolysins concerned in these processes appears to offer one of the most hopeful means of elucidating such obscure conditions. In the following pages the attempt will be made to show what results of practical value have already been obtained by the application of haemolytic methods on the lines indicated above, and also to suggest some of the problems which still await solution. Before proceeding to a review of these clinical aspects and applications of haemolysis, however, it is necessary to consider in some detail the character and mode of action of haemolytic agents. In this way alone will it be possible to arrive at a conclusion as to the significance of the results obtained by the various methods which have been employed.

Haemolysis. The Mode of Action of Haemolysins.

The nature of haemolysis. Haemolysis consists, to the naked eye, in the transformation of an opaque suspension of red blood corpuscles into a transparent haemoglobin-tinted solution. This alteration is due to the fact that the haemoglobin is no longer contained within the red corpuscles, but has diffused into the surrounding medium. A red blood corpuscle may be regarded as an envelope holding haemoglobin. The haemoglobin normally constitutes about one-third of the corpuscle, and almost all of the remaining two-thirds consist of water. The envelope, or stroma, which constitutes only 5 to 8 per cent. of the corpuscle, consists of protein material containing salts (principally of sodium in the case of carnivores and ruminants; of potassium in man, horse, pig, and rabbit) and lipoids—phospholipines (lecithins) and cholesterin. The envelope, in consequence of certain alterations, may become permeable for the haemoglobin, which then passes out.

Haemolytic agents. Haemolysis can be produced by a variety of agents both physical and chemical. Thus, distilled water, freezing and thawing, shaking, heating, ammonium chloride, dilute acids and alkalis, alcohols, ethers, soaps, fatty acids, the bile acids, mercuric chloride, some metals in the colloidal state (Ascoli), and certain glucosides, e. g. saponin, and alkaloids, as well as sera and plant and animal toxins, may all under suitable circumstances act as haemolytic agents. It is certain that these bodies do not all produce their effect in the same manner, although Nolf concludes that haemolysis in most cases depends on an alteration of the stroma of the red corpuscle which causes it to take up water; the 'hydrated' protein of the envelope is then permeable for the haemoglobin.

Water as haemolysin. Perhaps the most simple haemolytic agent is water. When water is added to blood the immediate effect is to produce a reduction in the concentration of salts (sodium chloride) in the medium surrounding the red corpuscles. Now the envelope of the red corpuscle is practically impermeable for NaCl, and when this crystalloid is present in sufficient concentration in the

medium surrounding the corpuscles the amount of water absorbed by the latter is limited, but on reducing the concentration of the salt in the surrounding medium the corpuscles absorb water, as is evidenced by the fact that they swell up, and if the dilution of salt be carried beyond a certain limit the corpuscles 'burst' and the haemoglobin diffuses out. The blood plasma of mammals in general exerts the same osmotic pressure, corresponding with that of the red corpuscles (but the correspondence between the osmotic pressures of the serum and the erythrocytes is not absolute—Moore and Roaf) and equivalent to the osmotic pressure of 0·9 per cent. NaCl solution, which is therefore termed isotonic or physiological salt solution. It is to be noted, however, that the resistance of the red corpuscle stroma to osmotic alterations is not constant in different varieties of animals, so that the degree of dilution which the red blood corpuscles will tolerate without diffusion of haemoglobin occurring is not the same throughout the various species. Thus in the case of blood corpuscles suspended in NaCl solution, normal human erythrocytes do not begin to haemolyse till the salt content of the fluid falls to 0·45 per cent., whereas haemoglobin begins to diffuse out of horse corpuscles when the concentration falls to 0·68 per cent.; in the case of ox blood the 'limiting concentration' of NaCl is 0·58 per cent.

The resistance of human red blood corpuscles to hypotonic salt solution may be investigated for clinical purposes in the following fashion (McNeil): To fifty million washed red cells suspended in 1 c.c. of 0·85 NaCl solution 1 c.c. of distilled water is added; then, after a suitable interval, the number of unlaked cells remaining is counted. McNeil found that the maximum degree of haemolysis occurred within twenty minutes and that lysis took place equally rapidly at 18° and at 37° C. Under the conditions observed 72–80 per cent. of the red cells from a normal subject underwent lysis. From these results it is clear that the resistance of all the red cells is not the same in any given specimen of normal human blood; but the proportion which resists haemolysis with the dilution employed is fairly constant in different individuals, so that an average index of resistance is thus obtained.

Like NaCl, other indifferent substances, e.g. neutral salts of sodium and potassium (KNO_3, NaBr, NaI, KI, &c.), and non-electrolytes, such as glucose and cane-sugar in iso-osmotic solution, also prevent haemolysis. It is found that the limiting concentrations of these substances for a given species of blood exercise the same osmotic pressure as the limiting concentration of NaCl, i.e. in a concentration which possesses an osmotic pressure equal to that of 0·9 per cent. NaCl the corpuscle envelope is impermeable for haemoglobin, and in the case of human red corpuscles haemolysis begins when the osmotic pressure of the dilution equals that of 0·45 per cent. NaCl. It is to be noted that the red corpuscle is comparatively impermeable for all the substances which are capable of forming isotonic solutions.

Urea. On the other hand, a substance which can freely permeate the red corpuscle envelope, such as urea, is incapable of constituting an isotonic solution

in any concentration; but urea does not by itself possess any haemolytic properties, since when it is added to a suspension of red corpuscles in isotonic solution no diffusion of haemoglobin occurs.

The other agents mentioned above all possess the property of causing haemolysis when added in suitable concentration to a suspension of corpuscles in isotonic solution.

Haemolysins of known chemical constitution. *Acids* and *alkalis* have a marked affinity for protein material, and their haemolytic action probably depends on the alterations which they produce in the protein of the stroma. Roaf holds the view that alkali and also elevated temperature may lead to haemolysis by raising the osmotic pressure of the haemoglobin within the red corpuscles, but he was unable to determine whether or not acid acted in the same way. The relation of the red cells to inorganic substances can be explained, Roaf thinks, without the assumption that the cell membrane will not allow these substances to pass through. Again, the organic bodies which possess haemolytic action, such as *alcohols*, *ether*, *soaps*, and *fatty acids*, all belong to the class of bodies which are termed *lipoid-soluble*, i. e. they dissolve in or are dissolved by certain 'fat-like' bodies. The lipoid-soluble bodies are supposed to enter into some sort of combination with the lipoids of the corpuscular envelope, which is thus 'poisoned' and rendered permeable for the haemoglobin. This theory of haemolytic action as due to lipoid solvents is further supported by the fact that in the aliphatic alcohol series increase in the number of carbon atoms is accompanied by an increase in lipoid solubility and also in haemolytic power. In the case of the unsaturated fatty acids, e. g. of the type of oleic acid, Moore has found that the haemolytic action is greater the higher the degree of unsaturation of the carbon atoms.

Saponin. The lipoid-solubility theory has also been applied to explain the action of haemolytic glucosides like saponin; thus, according to Arrhenius, when saponin is added to a suspension of red corpuscles in salt solution the glucoside is partitioned between the fluid and the corpuscles in a ratio of 1 to 120. A comparison of the susceptibility of different species of blood to haemolysis by hypotonic salt solutions and by saponin has shown that the order of sensitiveness in the one case is the reverse of that in the other. Thus, guinea-pig's corpuscles are comparatively insusceptible to hypotonic solutions, sheep's corpuscles are highly susceptible, and pig's are intermediate; in the case of saponin, sheep's corpuscles are least susceptible, guinea-pig's most sensitive, and pig's intermediate (Rywosch). These highly interesting observations suggest that the components of the stroma, on alterations of which the occurrence of haemolysis depends, are not identical in the two cases; so that saponin and hypotonic solutions probably measure two different functions of the stromata. A further point of interest is that a rough parallelism exists between the content of the corpuscles in phosphoric acid and their susceptibility to the action of saponin (Port).

Haemotoxins. Haemolysis is produced by a variety of toxins, i. e. bodies

originated by bacteria, higher plants, or animals, which are of unknown constitution, but are probably of protein nature. The mode of action of some of these has been determined with a considerable degree of certainty. Thus, in the case of certain snake venoms, e. g. *cobra venom*, the haemolysin results from the action of constituents of the venom on phospholipines (lecithin). As a consequence of this process an altered lecithin, the so-called *cobra lecithid*, is produced, which differs chemically from the original lecithin in containing fewer fatty acid radicles (*v.* Manwaring). Physical properties also distinguish the two bodies, as the lecithid is insoluble in ether and soluble in water, while the reverse is the case with lecithin. The lecithid is a most powerful haemolytic agent, whereas lecithin has very slight lytic effect. The blood corpuscles of certain species readily undergo lysis when cobra venom alone is added to them (e. g. man, rabbit, guinea-pig); others again do not haemolyse unless an emulsion of lecithin or the stromata of a susceptible species are added (e. g. ox, sheep, goat). The explanation of this is apparently that the phospholipines which are present in the stromata are differently combined in the two varieties of blood, being 'at the disposal' of the venom only in the case of the susceptible blood. Alcoholic extracts of insusceptible red blood corpuscles can supply the material necessary to enable the venom to cause lysis of insusceptible corpuscles, thus proving the presence of lecithin-like substances in the insusceptible stromata. The haemotoxins derived from animals (snake, scorpion, and bee venoms), plants (crotin), and bacteria (*tetanolysin* from the tetanus bacillus, *vibriolysin* from various spirilla belonging to the cholera group, *staphylolysin* from staphylococci) differ from the haemolytic agents already mentioned, since they all have the property when injected into animals of giving rise to *anti-substances*. The corresponding antiserum thus obtained has the power of combining with and so neutralizing the action of the haemotoxin. *Streptolysin*, the haemotoxin produced by pyogenic streptococci, appears to be a marked exception to this rule, since it has been found impossible to obtain antiserum by injections into animals (McLeod). Cholesterin has the property of inhibiting the action of a number of haemolytic bodies, e. g. saponin, cobra lecithid, and tetanolysin. Consequently its use has been suggested as a therapeutic agent in haemolytic anaemias.

Serum haemolysis. The sera of certain animals normally possess the power of lysing the blood of a foreign species. In other cases the haemolytic property is not normally present, but is acquired as the result of repeated injections of blood into an animal of different species. The immunization of a rabbit with ox blood corpuscles may be taken as an example of this process. Normal rabbit's serum has no effect on ox blood; but if a rabbit receives several intraperitoneal injections of ox blood its serum acquires the property of lysing ox corpuscles *in vitro*. An immune haemolysin has thus been developed in response to the injection of an 'antigen', which in this case is resident in the stroma of the ox red corpuscles. The process of serum haemolysis, however, is not a simple one. The effect of a haemolytic serum is due to the co-operation of a number of

factors. As will be seen later, alterations in each of the components involved may be of importance clinically. Accordingly, the process will be discussed more fully. The phenomena have been analysed with great precision in the case of immune haemolysins. As the test object a suspension of red blood corpuscles freed from serum by washing with 0·85 per cent. NaCl solution is usually employed. This is prepared by mixing defibrinated blood with several volumes of salt solution and then centrifugalizing; the supernatant fluid is removed and the sediment is shaken up with a further amount of salt solution, the whole process being repeated several times, until ultimately the blood corpuscles are obtained free from traces of serum; finally, a suspension equivalent to a 5 per cent. dilution of the original blood is made. If 1 c.c. of normal rabbit's serum is added to 1 c.c. of such a suspension of ox blood and the mixture is then incubated for an hour at 37°C. no alteration results. When, instead of normal rabbit's serum, the serum of a rabbit which has received several intraperitoneal injections of ox blood, *immune serum*, is employed it is found that haemolysis occurs. The immune serum is deprived of its haemolytic property by heating for one hour at 55°C.; but the difference between heated immune serum and heated normal serum is shown by the fact that a mixture of heated immune serum and fresh normal serum causes haemolysis, whereas a mixture of heated normal serum along with fresh normal serum is not haemolytic for ox blood. Thus, the occurrence of haemolysis is due to the co-operation of a relatively thermostable body present in the serum of an immunized animal, *immune body* (IB), which, as will be seen later, is specific for the corpuscles employed, along with a thermolabile body, *complement* (C), which is present in fresh serum, normal as well as immune (fresh normal serum is usually referred to as 'complement'). The complement does not become increased during immunization. The fundamental facts, mentioned above, which were originally demonstrated by Bordet, may be graphically represented in the fashion devised by Muir as follows:—

○ + fresh normal serum (C)	⋮	= no change.
○ + fresh immune serum	⋮	= haemolysis.
○ + immune serum 55° (IB)	⋮	= no change.
○ + IB + C	⋮	= haemolysis.
○ + normal serum 55° + C	⋮	= no change.

Where ○ represents the blood corpuscle and the dotted line indicates a period of incubation at 37° C.

Immune body has a marked affinity for the corresponding blood; Ehrlich and Morgenroth found that if red corpuscles are placed in contact with heated immune serum they anchor the immune body; thus when the corpuscles so treated are washed free from the serum and complement is then added to them haemolysis results at 37°C. Corpuscles which have anchored immune body are said to be *sensitized*. The high degree of affinity which exists between immune body and the corresponding red corpuscles is also shown by the fact

that combination occurs at 0°C. If red corpuscles are placed in a mixture of immune body and complement at 0°C. haemolysis does not take place; the immune body becomes fixed to the corpuscles, but the complement does not combine at this temperature. Accordingly, on testing the sediment and the fluid after effecting separation by centrifugalizing, it is found that all the immune body has become fixed to the corpuscles, while the complement remains free in the fluid. Immune body is specific in the sense that the antiserum obtained by immunizing an animal with the blood of a given species has no affinity for the blood of a widely different species; thus, for example, the immune body obtained by injecting a rabbit with ox blood has no affinity for guinea-pig's blood. But immune body has a certain degree of affinity for the blood of a species related to that employed in immunization; immune body for ox blood can act on sheep's blood. As has been seen, immune bodies are readily produced by injecting blood into an animal of different species; but it has been found experimentally by Ehrlich and Morgenroth that an animal does not produce an antibody to its own blood (*autolysin*), and an antibody to the blood of other individuals of the same species (*isolysin*) is not readily formed. This is an example of the general law that an immunity reaction is a response to the entrance of *foreign* protein directly into the tissues, or parenterally, as it has been termed. Accordingly, it is clear why an autolysin does not appear in the serum of an individual as a result of the absorption of extravasated blood.

Complement is an attribute of normal serum. It has little affinity for red corpuscles by themselves; but when the corpuscles are sensitized with immune body their affinity for complement is greatly enhanced. The complement then combines, most readily at 37°C. In addition to combining with sensitized corpuscles the complement acts on them like a toxin; and haemolysis is the obvious result of this toxic action. Complement and immune body react with the red corpuscles under quantitative conditions. Thus in order to effect haemolysis of a fixed amount of red blood corpuscles definite quantities of immune body and of complement are required. It has been found that the amount of immune body necessary to effect lysis of a fixed quantity of blood is reduced to a minimum when a certain excess of complement is present; but any additional increase of complement does not effect a further reduction in the haemolytic dose of immune body. In the same way, the haemolytic dose of complement is a minimum in the presence of excess of immune body.

In practice the minimum haemolytic dose (M. H. D.) of immune body is reckoned as the amount just sufficient to cause complete lysis of 1 c.c. of 5 per cent. blood suspension, e. g. of the ox, in one hour at 37° C. in the presence of excess of complement (0·1 c.c. fresh guinea-pig's serum). The M. H. D. of IB in the case of a fairly active immune serum for ox blood from the rabbit is 0·001 c.c. Similarly, the M. H. D. of complement is the amount of normal serum just sufficient to cause complete lysis of 1 c.c. of 5 per cent. blood suspension sensitized with 5 M.H.D. of IB. The M.H.D. of rabbit's C is on the average 0·05 to 0·2 c.c., and the M. H. D. of guinea-pig's C is 0·005 to 0·02 c.c. This difference

is due to the fact that guinea-pig's serum contains about ten times as much complement which is active in causing haemolysis as rabbit's serum.

Much more immune body and complement than the haemolytic doses can be fixed by the blood corpuscles; thus Muir showed in the case of ox corpuscles along with immune body from the rabbit and guinea-pig's complement, that an increase of immune body present caused a corresponding increase in the amount of complement which was led into combination. Complement which has combined with sensitized corpuscles is usually firmly fixed and cannot be recovered again. On the other hand, immune body is dissociable to a certain extent, so that red corpuscles which are introduced into the haemoglobin-tinted fluid which results after blood has been haemolysed by immune body and complement, become sensitized. The complements of the sera of different animal species may all be absorbed by red corpuscles sensitized with a given immune serum; but although the complements are alike in possessing the same combining apparatus, this does not mean that they are identical in other respects. As a matter of fact, the mass of evidence goes to prove that the complements of different animals are not identical, and further, that the complement of any given serum is not homogeneous.

Recent observations of Ferrata and others have shown that the complementing power of fresh serum is itself due to the interaction of several factors and is not simple, as was previously supposed. Thus, complement can be split up into fractions by the following procedure: The complement-containing serum is diluted with distilled water and is then acidulated (e.g. by passing carbonic acid gas into the solution), so as to precipitate a portion of the globulin, which is removed by centrifugalizing. It is found, then, that neither the globulin nor the fluid possesses complementing action, but the two when mixed together complement like the original serum. The globulin fraction is called middle-piece, since it is anchored directly by sensitized corpuscles; the residuum of the complement, end-piece, has by itself no affinity for sensitized corpuscles. As has been suggested above, it is necessary to distinguish between the combining affinity and the toxic action of complement. Complement may fail to produce haemolysis because (i) it does not combine with the sensitized corpuscles, or (ii) its toxic action is slight in spite of its having entered into combination. It has been found that, in general, serum complement has a relatively weak toxic action on cells of the same species, including the individual from which the complement is derived. In this we may detect a protective mechanism in case an immune body should obtain access to the circulation.

The action of a serum-haemolysin is essentially different from that of distilled water. Microscopic examination fails to detect any evidence of such a difference, since, in both cases, after the occurrence of laking, the stromata are seen to persist as 'shadows' which float in the clear haemoglobin-tinted fluid. But Bordet has shown that the stromata obtained by laking blood with distilled water retain their osmotic properties, so that on adding concentrated salt solution to the medium the stromata become crenated. On the other hand, when blood has

been lysed by a serum-haemolysin the stromata are found to have become altered in such a manner that they no longer respond to osmotic alterations; the addition of concentrated salt solution to the medium does not, then, lead to any alteration in the form of the stromata. The exact nature of the process involved in serum-haemolysis has not been determined, however. Certain workers (v. Liebermann, Bang) have suggested that either immune body or complement, or both, may be of lipoid nature. There is no conclusive evidence in favour of such views, although certain analogies exist between complement action and haemolysis due to fatty acids. Red corpuscles sensitized with immune body are under certain circumstances more susceptible to the haemolytic action of oleic acid than are unsensitized corpuscles; but this result obviously does not permit of the deduction that complement necessarily resembles a fatty acid in its constitution. Lipoids, however, may markedly influence the action of complement (Cruickshank and Mackie); and it is possible that complement may exist partly in an inactive condition in the serum and that lipoids may play a part in effecting conversion into the active state. The great importance of complement is due to the part which it plays in the production of immunity. Complement is essential for the bactericidal action both of normal and of immune sera, and the opsonic effect of normal serum on micro-organisms depends on the presence of complement. It has been held by Metchnikoff and his collaborators that complement does not exist normally in the blood plasma. The presence of complement in the blood serum is supposed to be due to its being shed from the leucocytes when these undergo phagolysis as the result of damage which they suffer when the blood coagulates. The weight of evidence, however, is in favour of the existence of complement in the normal blood plasma. Thus, if a portion of rabbit's blood is withdrawn from a vein and the corpuscles after being freed from serum are sensitized with immune body, it is found that the sensitized corpuscles when reintroduced into the rabbit's circulation undergo haemolysis, as shown by the occurrence of haemoglobinaemia and haemoglobinuria. If the washed corpuscles are not sensitized before reinjection no haemolysis occurs. Such experiments afford practically conclusive evidence of the existence of complement in the free state in the circulating blood. It must be borne in mind, however, that the conditions which hold *in vivo* and *in vitro* are widely different, and that there may be no quantitative parallelism between the processes under the two sets of circumstances. Muir and McNee in their experiments found that corpuscles sensitized with only a fraction of the dose of immune body necessary to cause lysis *in vitro* underwent extracellular solution in the animal's circulation. Also, in the body complement can apparently be rapidly renewed, since extensive haemolysis, which *in vitro* would lead to the using up of enormous amounts of complement, may occur in the circulation without leading to any marked diminution in the complement content of the serum. Another feature of haemolysis *in vivo* is that the immune body, after having led to the solution of the corpuscles to which it was attached, then becomes transferred to other corpuscles which similarly undergo lysis: the proof of this is afforded by the

fact that much more blood is destroyed than the amount which is introduced in the sensitized state, although barely a haemolytic dose of immune body had been added to the latter. The process of lysaemia also continues for several days, so that a true anaemia develops with the production of characteristic changes in the character and haemoglobin-content of the red cells.

As has been mentioned, the blood serum of many individuals normally possesses a greater or less degree of haemolytic action for the blood corpuscles of other individuals or other species. This natural lytic property has been shown in many instances to be due to the co-operation of complement with a natural immune body; but in certain cases the complex constitution of the natural haemolysin has not been definitely established. The occurrence of natural immune bodies in the serum must be regarded purely as a metabolic accident and devoid of any teleological significance. Thus, the serum of many guinea-pigs contains a natural immune body for ox red corpuscles. In addition to its power of complementing haemolytic and other immune bodies, fresh serum normally possesses other similar properties, e. g. the addition of fresh serum enables cobra-venom to haemolyse certain species of blood which are not susceptible to the venom by itself. This venom-activating property of fresh serum is certainly not due to lecithin, but resembles complement, although it is not identical with the complement which acts with haemolytic immune body (Browning and Mackie).

There is no very conclusive evidence with regard to the *sites of origin in the body of immune body and complement*, although the haemopoietic organs and vascular endothelium in general are credited with their production. In this connexion Müller's observations on the increased formation of immune body and complement as the result of thyroid feeding are of much interest.

The effect of haemolytic agents on the stromata varies, as has been mentioned: after lysis by water, serum, and saponin the stromata persist as shadows; on the other hand, the bile acids and cobra lecithid dissolve the stromata.

In the preceding pages a number of properties of the various constituents of the blood which may be concerned in haemolytic processes have been described. Each of these is susceptible of variation, and the alterations are in many cases associated with particular disease conditions or have a direct bearing on problems of clinical interest. Accordingly, in subsequent sections the following questions will be considered: (i) alterations during disease in the resistance of the red corpuscles to haemolytic agents; (ii) the clinical significance of variations in the serum and other tissue fluids as regards (*a*) complement content at different ages and in disease, (*b*) content in immune body, isolysins and autolysins (paroxysmal haemoglobinuria), (*c*) power of aiding or inhibiting certain haemolytic processes; (iii) the detection of antigens and antibodies in the tissues and tissue fluids by means of the reaction of 'deviation of complement' (Wassermann reaction, &c.); (iv) the relation between known haemolytic processes and certain clinical conditions characterized by blood destruction—the so-called haemolytic anaemias and blackwater fever.

Alterations in the Resistance of Red Corpuscles to Haemolytic Agents.

The resistance of the red corpuscles to laking agents under various disease conditions has been widely investigated. It is important that the red cells which are to be tested should be completely freed from serum. Serum exerts a modifying effect, which is variable, on the action of most haemolytic bodies. McNeil studied the resistance of the red cells to saponin and to hypotonic salt solution simultaneously. He worked in every instance with a fixed number of red corpuscles freed from serum and suspended in a constant volume of fluid. In the case of saponin, the degree of haemolysis produced by two amounts was determined, the larger being sufficient to lyse 84–93 per cent. of the quantity of red cells employed from a normal person,[1] and the smaller amount producing 7–23 per cent. of lysis of normal corpuscles. It is clear that the larger amount of saponin served to detect increased resistance of red corpuscles, since the resistant corpuscles would not be lysed by an amount of saponin sufficient to dissolve normal blood; on the other hand, the small amount of saponin tested diminished resistance through the occurrence of more than the usual amount of lysis with this quantity. It was found that the resistance of the red corpuscles to saponin was diminished to the greatest extent in cases with high fever (acute miliary and pulmonary tuberculosis, very acute typhoid fever); great diminution occurred also in deep and persistent obstructive jaundice. In anaemic cases there was diminution of resistance which was most marked in severe and progressive pernicious anaemia; but there was no distinctive difference between more chronic, less severe cases of pernicious anaemia and other severe anaemias. The resistance to saponin was increased in diabetes and in cases of moderate fever (lobar pneumonia, influenza, tuberculosis). It was noted, however, that in these cases of fever the amount of lysis produced by the smaller amount of saponin was greater than with normal blood, i.e. there was increased lability of the 'low resistance group' of cells. The results with hypotonic salt solution in jaundice were directly the opposite of those with saponin; thus the resistance to hypotonic NaCl solution was increased in this condition. In this connexion McNeil pointed out that in jaundice the plasma is hypertonic, and he showed experimentally that corpuscles which have been treated *in vitro* for some time with slightly hypertonic salt solution become less susceptible to lysis in hypotonic salt solution, but their resistance to saponin remains unaltered. Heuberger and Stepp, however, in contrast to McNeil and others, hold that the resistance of the red corpuscles to saponin in disease remains constant. The resistance to hypotonic salt solution is increased in icterus neonatorum

[1] This degree of haemolysis was chosen for technical reasons, because it was found that the amount of saponin required to produce 99 per cent. of lysis was about twice as great as that which sufficed to produce 90 per cent. of lysis. Evidently, as haemolysis approached completion some powerful retarding factor came into operation. Accordingly, by choosing as the end-point 7/8-9/10 lysis, disturbances due to the retardation factor could practically be excluded.

(Slingenberg) and after venesection (Snapper, Oczesalki and Sterling). In contrast to obstructive jaundice, it was found by Chauffard that the resistance of the red cells to hypotonic salt solution is, as a rule, decreased in congenital and in acquired haemolytic jaundice (v. Stejskal, Massaglia and Tarabini, Pel, Maliwa, Roth); in these conditions the resistance to bacterial haemotoxins and to lipoidal haemolysins is also reduced, according to some observers.

In the new-born, Slingenberg found the resistance of the red cells to hypotonic salt solution equal to that of the adult; the resistance then underwent an increase till the third or fourth day after birth and thereafter diminished till the tenth day.

The haemolytic effect of cobra venom on red corpuscles shows considerable variation under different conditions. Weil found the resistance increased in cases of syphilis. This has been confirmed by Kraus, Pötzl, Ranzi and Ehrlich; increased resistance was observed also in carcinoma (Kraus, Graff and Ranzi) as well as in dementia praecox (Hirschl and Pötzl). Red cells from the umbilical vein are more resistant than normal, whereas those of the pregnant woman are less resistant (v. Graff and v. Zubrzycki). Stone and Schottstaedt have repeated Weil's work and consider that the determination of the resistance of the red corpuscles is superior to the Wassermann reaction for the detection of cases of latent syphilis, in 78 per cent. of which they obtained a positive result by Weil's method (see also Schwartz).

The behaviour of the red cells with a specific serum haemolysin has been investigated by Rous, who found the resistance very constant with normal blood and in secondary anaemia, but increased in haemophilia and in a case of congenital haemolytic icterus, and reduced in two out of three cases of pernicious anaemia. Rous found also that the resistance to serum haemolysin and to hypotonic salt solution did not run parallel. In obstructive jaundice the resistance to serum haemolysin was reduced in three out of nine cases, but not in a marked degree.

Except in the case of haemolytic icterus, it cannot be said that the extensive investigations on alterations in the resistance of the red corpuscles have led so far to any definite conclusions as to the significance of the phenomena. This is due partly to the fact that most observers have studied the effect of only one or two haemolytic substances instead of correlating the action of many of such bodies, and also to the lack of knowledge in most cases as to what components or functions of the corpuscles are really being measured. Port, McNeil, and others have considered that the resistance to saponin is a measure of the red corpuscles' content in cholesterin; but this does not seem to have been definitely proved in disease. The highly important rôle of the red corpuscles in contributing to the requirements of the tissues as a whole makes it clear that other alterations in these elements beyond their content in haemoglobin merely must have very far-reaching effects in the body, and justifies the conclusion that further research on the biochemical properties of the erythrocytes will have fruitful results.

Variations in Serum Complement.

According to Ehrlich, the co-operation of immune body and complement in producing lysis of bacteria and red corpuscles is a process analogous to that which occurs in nutrition. Immune body in the form of a 'receptor' attached to the cell protoplasm, i.e. 'sessile', is supposed to effect the anchoring of food molecules of relatively large size to the protoplasm; then the conversion of the food-stuff into material available for the nutrition of the cell is supposed to be brought about by the ferment-like action of complement. Pfaundler, proceeding on this hypothesis, suggested that the content of the serum of infants in complement might serve as an index of their capacity for utilizing satisfactorily artificial nutriment and of their powers of resisting infections; the observations of Moro appeared to establish such relationships. The question was very thoroughly investigated by Findlay, Fua and Noeggerath. As a result of the examination of ninety-eight cases by accurate quantitative methods these workers found that the complement content of sucklings' sera was in general a function of age rather than an index of capacity to utilize nutrition. The complement content of the serum was least just after birth and the increase in complementing power was especially marked during the first three months of life. Exceptional results were, however, met with, for which no adequate explanation could be given. Thus in the case of three infants all suffering from a similar form of dyspepsia, two were tested when eight to nine weeks old, after rearrangement of diet had caused marked improvement; the one showed a good complement content in its serum, the other a very poor complement content. The third was tested when three weeks old, while ill with dyspepsia, and showed no complement in its serum, but thereafter it progressed very favourably on foreign nutriment. The complementing power of the serum of many of the cases investigated by these workers was also tested simultaneously on two different species of blood corpuscles, viz. sheep's and guinea-pig's (heated adult human serum being used as the source of immune body), and they found that parallel results were not always obtained in the two series. This divergent behaviour is in complete correspondence with the variations obtained in testing the sera of adults and of animals in general. Many observers have found that the complement content of human sera, as tested with a number of immune bodies, shows wide variations which are within normal limits (Marshall and others), although Gunn's recent examination of the complementing power of twenty-three subjects, including healthy adults or patients far advanced in convalescence, for ox corpuscles fully sensitized (with five doses of immune body from the rabbit) gave very uniform results (the lytic dose of serum for 1 c.c. of blood suspension varied between 0·17 and 0·3 c.c., and the mean dose was 0·21 c.c.); and this result agrees with Backman and Jacobaeus. Digestion does not appear to have any marked or constant effect on the complement content of the serum (Gunn, Ssirensky and Nawrozky), nor does the complementing power vary markedly from day to day in a healthy adult. In many more or less chronic

diseases variations similar to those noted in health occur, to which no significance can be attached, e.g. in syphilis. Popoff, however, finds that in syphilis the blood serum lacks the power of haemolysing guinea-pig's red corpuscles, whereas this property is constantly present in marked degree in the sera of healthy individuals and in other diseases. He attributes this result to deficiency of complement in syphilitic serum. Similarly, it has been stated that the serum is devoid of complement in leprosy (Eliasberg). In cases of malignant tumour the complement content of the serum bears no relation to the cachectic state of the patient (Engel). The content of the serum in complement at various stages of acute infectious diseases has been made the subject of an extensive study by Gunn.[2] The complementing power of the serum was tested from day to day in cases of enteric fever, erysipelas, diphtheria, scarlet fever, measles, typhus fever, and pneumonia, using for the test ox corpuscles sensitized with immune body from the rabbit. The results obtained in enteric fever were striking. Thus, it was found that (1) complement is more abundant during the period of pyrexia than during convalescence; (2) the fall in complement content occurs most rapidly in those cases in which the period of fever has been of short duration; (3) the amount of complement present in the serum during the stage of fever bears some relation to the severity of the attack; thus complement may be deficient in cases which are very ill, and patients who are slightly ill also have a moderately small amount of complement in their serum; but in cases of considerable severity, which are the most common, a large amount of complement is found as a rule; (4) increase of complement occurs during relapses, and when recovery again takes place the complement diminishes sooner than after the original attack; (5) complement may or may not be very abundant in fatal cases, and Bordet's view is confirmed that death in infections is not due to an insufficiency of complement. In pneumonia and in diphtheria the complement in the majority of the cases was increased during the stage of acute illness and diminished in convalescence. In several fatal cases of diphtheria, including a haemorrhagic case, the complement content of the serum was relatively great two days before death. On the other hand, in some cases of severe and of moderately severe types the complement was small in amount or practically absent during the acute stage. In six cases no variation in the amount of complement was observed during the presence of serum-rashes; this is interesting in view of the relation of such phenomena to experimental anaphylaxis. Anaphylactic symptoms are said to be accompanied by a diminution in the serum-complement, and Fornario, in contrast to Gunn, found a diminution in the complement of patients suffering from serum-disease following a single injection of foreign serum. In erysipelas the results tended in the direction of an increase of complement during the acute stage, but this was not constant. Prolonged suppuration following erysipelas was, however, accompanied by an increase in the complement. The amount present in fatal cases of erysipelas was above the average. In scarlet fever complement tended to be diminished towards the end of the fever

[2] I am indebted to Dr. Gunn for permission to quote his unpublished thesis.

and to increase during convalescence. The results, however, were somewhat indefinite; but the complement was markedly diminished during nephritis. In malignant scarlet fever at the time of death the complement was increased. Gunn's observations are in agreement with the results of other workers; thus Breton, Massol and Minet, as well as Ssirensky, found that the serum complement was increased in febrile states in general, e.g. in pneumonia, erysipelas, and typhoid fever. The increase in the complement which acts along with immune body to produce haemolysis is possibly a result merely of the alteration in metabolism which occurs in acute diseases and of which elevation of temperature is one of the most evident signs. There is no good ground for supposing that the content of the serum in 'haemolytic' complement affords an index of an individual's power of specific resistance or reaction to infection. So far as *in vitro* experiments can show, the bactericidal action of normal serum depends on the presence of a comparatively minute amount of bacteriophilic complement, which can be removed by treating the serum with small amounts of bacteria, and very minute quantities of organisms of one variety remove from the serum its bactericidal action for other species of bacteria. The treated serum, which is then quite inert so far as normal bactericidal action is concerned, is found to have suffered little or no diminution in its power of complementing haemolytic immune body and of causing bactericidal action along with a specific immune serum (Muir and Browning). The bactericidal power of the blood plasma is undoubtedly an important factor in the resistance to many infections, and a systematic investigation of the variations in bactericidal property both as regards complement and immune body content may be expected to afford important information as to resistance to infection in general, although such work would be extremely difficult to carry out.

The Content of the Serum in Natural Immune Bodies.

Normal human serum may contain natural immune bodies for various species of blood. Aschenheim and others have found in human serum natural immune bodies for the red corpuscles of rabbit, guinea-pig, goat, sheep, horse, pigeon, pig, and ox. The content of the serum in such immune bodies varies in different individuals and also in the same individual at different times, but they are not dependent on the state of nutrition (Backman and Jacobaeus). Aschenheim found an increase in immune bodies during fevers. Gewin made a thorough study of the natural lytic immune body for sheep corpuscles in the blood of infants. He found that the immune body was never present in the serum at birth. Immune body appeared in the blood of healthy infants, especially those fed at the breast, during the second half of the first year of life; on the other hand, artificially fed or unhealthy infants showed the immune body in their serum in the first few months. Thus the content of the serum in immune body for sheep's blood depended definitely on ill health and malnutrition. These results, however, did not apply generally to all natural

haemolytic immune bodies, since immune body for rabbit's red corpuscles was found occasionally in the serum in considerable amount at birth, when no sheep immune body was present. Again, at later dates (nine months), rabbit immune body was absent in cases where abundant sheep immune body existed in the serum. It might be thought that the appearance of an antibody to sheep's blood in infants was an immunization phenomenon due to the ingestion of cow's milk, since it is known that (1) in infants protein taken into the alimentary canal may find its way unchanged into the circulation and there act as antigen, (2) injections of milk can give rise to the development of haemolytic immune bodies, and (3), ox and sheep being closely allied species, their tissue products contain antigens in common, so that an immune body for ox blood acts with sheep's red corpuscles and vice versâ. Possibly in some cases the origin of the immune body may be explained in this way, but the important fact is that the anti-sheep immune body, as Gewin found, was marked in the serum of some children who had been fed exclusively on human milk. Gewin concludes that infection is the factor which determines the early appearance of immune body in the serum, and this agrees with the observation that in the course of an infection such as typhus fever antibodies (agglutinins) may appear in the serum for B. typhosus, which is not causally connected with the disease at all (Wilson). Attempts have been made to demonstrate an increase in various natural immune bodies in the serum in cases of cancer. Thus, Kelling considers the power of lysing hen's red blood corpuscles as of diagnostic importance, and especially as a valuable indication in cases of cancer of the alimentary canal; but according to Kraus results of practical value are not obtained.

The Presence of Haemolysins in Cerebro-spinal Fluid, Exudates, &c.

Kafka has made very interesting observations on the presence of natural immune bodies in the cerebro-spinal fluid. Normally the cerebro-spinal fluid contains neither immune body nor complement. In ninety out of ninety-eight cases of general paralysis Kafka found immune body for sheep's corpuscles in the cerebro-spinal fluid, and in cases of meningitis the immune body was also present almost constantly. On the other hand, no immune body occurred in the fluid of twenty-five cases of syphilis and cerebral syphilis, although in the latter condition the fluid contained abundant protein. In sixty-one other cases, including tabes, multiple sclerosis, and various psychoses, no immune body was found in the cerebro-spinal fluid. Traces of complement were also present in the cerebro-spinal fluid of 10 per cent. of the cases of general paralysis in which immune body was found. Complement was much more frequently present and more abundant in the fluid in meningitis. Variations in the immune body content of the fluid were met with at different times and usually ran parallel with variations in the serum; but immune body might be present in the fluid and absent from the serum. Repeated puncture in itself did not affect the amount of immune body or complement present in the spinal fluid. Normal

immune bodies and complement occur in exudates and transudates (Marshall). Mutermilch and Hertz found passive transudates poor in complement as compared with the serum; serous inflammatory exudates were almost as rich in complement as serum; but complement was absent from purulent and seropurulent exudates (complement was tested for both by haemolytic and by bactericidal experiments). Apparently only small amounts of complement are present in fresh milk, but no significance can be attached to this fact as regards the nutritive value of the milk, since the complement will be destroyed in the stomach (Lane-Claypon, Kolf and Noeggerath); normal immune bodies may also occur in this fluid. The aqueous humour does not normally contain complement and only traces of immune body; but these substances are present in the fluid which collects after puncture (*v.* Mijashita, Tschirkowsky).

Isolysins.

The fact that the serum of one individual may be able to cause haemolysis of the red blood corpuscles of another member of the same species *in vitro* (*isolysis*) has long been observed. Elsberg, Neuhof and Geist, and others, have investigated isolysis by injecting blood suspension subcutaneously into another person, the occurrence of lysis being shown by the development of a reddish-brown or blue discoloration (Gorham and Lisser). Heating at 55°C. deprives the serum of its haemolytic effect *in vitro*. Isolytic action is probably due to the co-operation of complement along with a natural immune body, since Ascoli and Moreschi, and others, have succeeded in restoring the effect by the addition of complement to heated isolytic serum. The investigation of isolysins in the human subject has been extensively pursued in the hope that their occurrence might be of clinical importance. As to the reason for the development of isolysins, no satisfactory explanation has been offered. Some observers have concluded that isolysins for the red corpuscles of normal individuals were specially frequent in the serum of patients affected with carcinoma.

Crile, from the examination of a large series of cases, concluded that the occurrence of isolysin in a patient's serum afforded additional evidence in the diagnosis of early cancer, although not specific for that condition. In cases of tuberculosis Crile found the red corpuscles specially susceptible to the isolytic action of normal sera.

The results of different workers have been contradictory, however. Gräfe and Graham, as will be seen, have arrived at results which are diametrically opposed to those of Crile. They have pointed out that in work of this kind it is necessary to ensure that the red corpuscles employed as the test object are really susceptible. Proceeding on lines already laid down by Landsteiner and Leiner, and von Dungern and Hirschfeld, Gräfe and Graham have shown that it is possible to select two individuals such that the serum of each will lyse the red corpuscles of the other; but, of course, the serum of each has no effect on its own corpuscles (see also Bürger). This may be

schematically expressed by saying that Individual I possesses corpuscles of type A which are lysed by serum *a* belonging to Individual II, and conversely that Individual II possesses red corpuscles of type B which are lysed by serum *b* belonging to Individual I. Thus, lysis will occur only when corpuscles containing the receptor A meet serum *a* or when corpuscles containing the receptor B meet serum *b*. Now, on extending the observations to the blood of a series of individuals it is possible that in any instance the red corpuscles may contain (1) A alone, (2) B alone, (3) A and B, (4) no receptor, or (5) receptors which are neither A nor B. Similarly, the serum may contain (1) *a* alone, (2) *b* alone, (3) *a* and *b*, (4) no isolysin, or (5) isolysins which are neither *a* nor *b*. It can be said, to begin with, that no evidence was found of the existence of receptors other than A and B; also the presence simultaneously of a given receptor in an individual's red corpuscles, and of the corresponding lysin in his serum, is the rarest possible occurrence, so that autolysis very seldom occurs. With these exceptions the properties of the red corpuscles and the properties of the serum can be associated in any one individual in any of the possible groupings. Gräfe and Graham examined 99 cases which included the following conditions: normal, 11; acute infections, 17; tuberculosis, 21; syphilis, 6; carcinoma, 20; blood diseases, 5; chronic diseases not already specified, 19. They found that the red corpuscles of normal persons were most frequently susceptible to isolysis (7 susceptible out of 11 cases), and those of tuberculous individuals were the most resistant (only 5 being susceptible out of 21), but the number of cases examined was not sufficiently large to permit of a definite conclusion. As regards the properties of the serum, isolysins were as frequent in healthy individuals as in cases of carcinoma or tuberculosis. The observations extended over some months, and while the isolytic power of the serum was found to vary, the corpuscles remained constant in their susceptibility and in the type of receptors which they contained. It is evident, therefore, that the investigation of isolysins, while of great interest for biological and biometric studies, especially as regards the hereditary transmission of characters, possesses so far little or no definite diagnostic value in disease, although Gorham and Lisser hold that the occurrence of haemolysis *in vivo* is sufficiently significant for the diagnosis of carcinoma to warrant a wide application of the test. With regard to the presence of isolysins in the serum as bearing on the transfusion of blood, Crile states that haemolysis may occur *in vitro*, but not *in vivo*. Gorham and Lisser have made the same observation in connexion with subcutaneous injections of red corpuscles, and have also met with the converse condition, lysis *in vivo* but not *in vitro*. Schultz found in one instance that the injection of 50 c.c. of blood, the serum of which had iso-agglutinating and isolytic action on the patient's red corpuscles, caused symptoms of collapse with rigor and slight oedema of the face and hands; but in another case similar phenomena occurred, although no isolysins could be demonstrated *in vitro*. In the latter instance it is possible that natural antibodies other than haemolysin were present in the serum, and thus led to the phenomena of anaphylactic character. Suitable

individuals whose serum was without isolytic action and whose blood corpuscles contained receptors of only one type might be used for the determination of blood volume according to a method devised by Todd and White. These workers introduced into cattle a given amount of blood of other oxen and then determined the quantity of the foreign corpuscles present in a sample of the blood of the injected animal by means of an immune isolytic serum which acted only on the foreign red cells. In the case of the human subject corpuscles of the type opposite to his own would require to be injected, and then the test would be carried out with a specimen of human serum which lysed only the injected corpuscles.

Autolysins.

As has been mentioned, it is only very rarely that a person's serum has the property of lysing his own blood corpuscles, i. e. contains an autohaemolysin. Of course, the term autolysin should not include lytic action due to the presence of bacterial toxins in the blood, e. g. in cases of streptococcal septicaemia, but applies to products of the activity of the tissues. Gräfe and Graham found an autolysin in the serum of one of their cases, a woman suffering from chronic nephritis with heart failure. The autolysin was not constantly present, being detected only twice out of four examinations undertaken over a period of a month. In a case of icterus, probably carcinomatous, Dudgeon found distinct autohaemolytic action of the serum. Simpson investigated fifty cases of malaria, mainly of the malignant tertian type. In four instances an autolysin was found ;[3] three of these were simple tertian, all untreated with quinine. In two of the latter the reaction occurred with the serum withdrawn in the premonitory stage of the attacks, i. e. when young sporulating forms were being set free in the blood, and the reaction disappeared when fever was established. In the third case the lysin appeared shortly after the preliminary stage. Only one case of malignant tertian fever showed an autolysin in its serum. A case of black-water fever showed isolysin (no mention of autolysin is made in this instance). In twelve out of fifty cases of advanced tuberculosis of the lungs Vogt demonstrated the occurrence of lysis when a specimen of the patient's blood, prevented from clotting by the addition of potassium oxalate, was incubated at 37° C. In these cases cooling of the mixture previous to incubation did not lead to any increase of the haemolysis. Negative results were obtained with the blood in fourteen cases of early phthisis, nine cases of scarlet fever, and ten cases with various mild illnesses. The mechanism of the haemolysis observed by Vogt is not clear, however. It is to be noted that certain persons possess markedly labile red corpuscles. Thus, an apparently normal individual is known to the

[3] It is not clear whether the autolysins observed by Simpson are of the nature of immune haemolysins or whether they are haemotoxins produced by the malarial parasites; but his observations on cases of malignant tertian malaria show that the number of corpuscles destroyed may be 25 to 35 times the number containing parasites.

writer, whose serum when it separates spontaneously from blood-clot is always deeply tinted with haemoglobin; but his serum does not contain an autolysin, and he does not give a positive Donath-Landsteiner or a positive Wassermann reaction. The action of an autolysin within the body would obviously lead to anaemia. This possibility as an explanation of certain forms of anaemia will be discussed later.

Paroxysmal Haemoglobinuria.

The existence of a peculiar form of autolysin in the serum of cases of paroxysmal haemoglobinuria *e frigore* has now been definitely established in many cases. The fact that haemoglobinaemia precedes the haemoglobinuria was demonstrated by Ehrlich in 1881. A finger of the patient was ligatured at the base with an elastic band; the finger was then immersed for fifteen minutes in ice-cold water and thereafter in warm water. Blood was then withdrawn into a capillary tube and allowed to clot. The serum which separated out contained haemoglobin; that from an unchilled finger did not. Microscopic examination of blood from the treated finger showed shadows, i.e. stromata from which more or less of the haemoglobin had diffused out; thus a process of haemolysis had occurred. Ehrlich also recognized that the haemolysis was not due to special susceptibility of the corpuscles to cooling. A further advance in the knowledge of this condition was made independently by Eason and by Donath with Landsteiner, who showed that the haemolysis of the patient's or a normal person's red corpuscles in the presence of the patient's fresh serum occurred *in vitro* when the mixture of serum and red cells was first cooled and then incubated at 37° C., the preliminary cooling being essential (the Eason-Donath-Landsteiner phenomenon). The haemolysin is of complex constitution, like the immune haemolysins already described; thus the haemolytic action is due to the co-operation of immune body and complement. The immune body of the paroxysmal haemoglobinuric's serum is peculiar in this respect, that it combines with the red corpuscles only at a low temperature, but not at 37° C. The suitable complement is present in any human serum, normal or other. It acts only at or near body temperature. Thus haemolysis is due to the toxic action of complement which combines at 37° C. with red corpuscles already sensitized as the result of their anchoring the immune body at a lower temperature. In the process of haemolysis complement is used up. The serum of a haemoglobinuric shortly after an attack frequently contains little or no complement, so that the Eason phenomenon fails to occur *in vitro* with the patient's serum at this period unless complement in the form of fresh serum (human or animal) is added. The absence of complement, however, does not cause the attacks to cease. This is explained by the observations of Meyer and Emmerich, who found that although the blood after an attack lacked complement, if a finger was ligatured and exposed to cold, according to the procedure of Ehrlich, then blood from that particular finger alone contained complement, which had been derived in some way from the tissues *in situ*. Similarly Moro, Noda and Benjamin found that in their case, just before a cold

foot-bath which caused an attack of haemoglobinuria, there was little complement in the serum; fifteen minutes later the serum contained much complement, but one hour afterwards complement was entirely absent. Browning and Watson, and also Cooke, have found that the red corpuscles at 0°C. remove from the haemoglobinuric's serum not merely the immune body, but also certain constituents of the complement, so that the treated complement is no longer able to lyse a haemolytic system (ox red corpuscles sensitized with immune body from the rabbit). The component of the complement fixed in this way was found not to be identical with the complement middle-piece obtained from human serum by means of precipitation with carbonic acid gas.

When the sera of other individuals or of animals are used as the source of complement, it is essential to ascertain by control experiments that these sera do not by themselves exert any haemolytic action on the corpuscles.

Very considerable variations exist in the properties of the haemolysin in different cases. Thus, the depression of temperature necessary to enable the immune body to combine with the corpuscles, as judged by the degree of cooling required before haemolysis, will occur subsequently at 37° C., varies markedly. In some instances room-temperature suffices, in others the mixture of serum and blood corpuscles must be placed at 0° C. in order that haemolysis may occur later at 37° C. Clinically also, marked differences are observed in the degree and duration of chilling necessary to produce an attack of haemoglobinuria. The proof that the haemoglobinuric haemolysin is an immune body-complement haemolysin analogous to that of experimental immune sera can be most satisfactorily established by showing that the specific immune body persists in the serum after the complement has been destroyed by heating at 55° C. Some observers have found this to be the case; others again (Widal and Rostaine) have found the heated serum devoid of sensitizing action. Moss, as the result of his observations, considers that intact complement must be present in order to enable the immune body to combine with the red corpuscles. In the experiments of Moss the red corpuscles did not become sensitized on exposure to heated haemoglobinuric serum at 0° C.; but if the corpuscles were treated with a mixture of heated haemoglobinuric serum and fresh normal complement-containing serum at 0° C., then sensitizing occurred. Two cases examined by Browning and Watson illustrate the variations in the thermostability of the haemoglobinuric immune body. Thus the serum of one case (A) when deprived of its lytic action by heating for half an hour at 55° C. still contained immune body, since red corpuscles treated at 0° C. with the heated serum and then washed and placed in contact with normal serum underwent lysis at 37° C. On the other hand, the heated serum of case B possessed practically no sensitizing action, even on adopting the procedure followed by Moss. The haemoglobinuric immune body which has become fixed to the red cells in the cold tends to dissociate again at higher temperatures. This is shown by the fact that red cells sensitized by exposure to serum at 0° C. and then freed of serum and digested with 0·85 per cent. NaCl solution at 37° C. for some time, no longer

become haemolysed on the subsequent addition of complement (Moro, Noda and Benjamin). Apparently the immune body has dissociated from the corpuscles at 37° C., but the fluid in which the corpuscles have been digested is not capable of sensitizing a further amount of red corpuscles at 0° C. The dissociability of the immune body varies, however; thus the immune body in the serum of case A did not dissociate to any appreciable extent, whereas that of case B showed the phenomenon of dissociation when the patient's own corpuscles were employed, but not with the red cells of another person (Browning and Watson). A considerable number of observers have failed to obtain the haemolytic phenomenon *in vitro*, and the view has been advanced that the mechanism of haemolysis in the test-tube does not throw any light on the nature of the process occurring in the body of the haemoglobinuric patient. Further, autolysins have been observed in the blood of general paralytics, who have never been affected with haemoglobinuria (Donath and Landsteiner). With regard to failures to elicit the phenomenon, a number of possible fallacies must be excluded, viz. (1) the serum of haemoglobinurics after an attack is devoid of complement, which is essential for the production of haemolysis *in vitro*; (2) the immune body may combine with the red cells at a comparatively high temperature (20° C.) and so be removed from the serum by the red corpuscles in the clot; accordingly the serum which is to be tested must be obtained by allowing the patient's blood to clot at 37° C.; (3) the haemolytic power may disappear rapidly from the serum after the blood is shed, so that the serum is inactive after it has been kept for twenty-four hours; accordingly the action of the serum should be tested within a few hours after the blood has been withdrawn; (4) when the corpuscles are kept in contact with the active haemoglobinuric serum for twenty-four hours at a low temperature (in the ice-chest) haemolysis may fail to occur subsequently at 37° C., although a specimen of serum kept separately is still lytic; (5) the proportion of serum to red corpuscles must be suitably adjusted in order that haemolysis may occur *in vitro*; if too large an amount of red cells relatively to serum is present, then the action of the haemolysin is lost by its being distributed over all of the corpuscles, none of which are sufficiently damaged to undergo lysis;[4] (6) a small amount of immune body, which can produce haemolysis in the body, may escape detection in test-tube experiments.

There is no basis for the assumption that the process of haemolysis must take place in the circulation under the same quantitative conditions as in the test-tube. In fact, as Muir and McNee's experiments have shown, haemolysis *in vivo* occurs probably to a much greater extent than the estimation of the haemolytic power of the serum *in vitro* would indicate. Accordingly, failure to obtain a positive haemolytic effect *in vitro* does not afford any conclusive evidence as to the absence of a haemolytic mechanism such as that described, and there is no good reason for regarding the presence of the autolysin in the

[4] 0·2 c.c. of serum to 0·005 c.c. of washed blood has been found to be a suitable combination in a number of cases.

blood of haemoglobinurics merely as the result of blood destruction in the body and as unconnected with the causation of the attack. Widal and Rostaine have suggested that the real alteration in the haemoglobinuric's serum is the absence of an antihaemolysin, which is constantly present in normal serum; but on the basis of experiments this appears unlikely (Donath and Landsteiner). It is not known whether, as *in vitro*, only those red corpuscles which have been exposed to the cooling process by passing through the chilled part of the body subsequently undergo lysis, or whether, perhaps, in some way so far unknown, the sensitizing process spreads to red cells which have not been cooled. Attempts to determine the existence of abnormalities in the resistance of the haemoglobinuric's red corpuscles to haemolytic agents such as hypotonic salt solution, saponin, variations in temperature, acids, &c., have led only to contradictory results. It is a remarkable fact that the haemolysin may persist in the serum long after attacks of haemoglobinuria have ceased to take place; thus Browning and Watson observed one case which showed an active haemolysin although no attack of haemoglobinuria had occurred for two and a half years. This circumstance, along with the observation of the presence of autolysins in the serum of cases which have never been attacked by the disease, shows that other factors, in addition to the presence of the lysin, are required to induce the haemoglobinuric attacks. The chief auxiliary factor appears frequently to be vasomotor disturbances of Raynaud type, which lead to a local depression of temperature sufficient for the immune body to combine with the red corpuscles. As will be seen later, syphilitic infection is practically a constant forerunner of paroxysmal haemoglobinuria *e frigore*. How syphilis conduces to the development of autolysins is, of course, so far quite unexplained. The mechanism of blood destruction in the more rare types of paroxysmal haemoglobinuria has not yet been cleared up, e.g. in the cases of attacks following exercise. Van den Bergh's observation that the presence of carbonic acid gas sometimes leads to haemolysis of haemoglobinurics' blood may throw some light on the obscure phenomena. The experiments of Fejes on horses are most interesting in this connexion. He withdrew 1,000 c.c. of blood and reinjected subcutaneously the separated and washed red corpuscles. This procedure was repeated a number of times in normal animals, but led to no formation of haemolysin. Severe exercise or infection with *Trypanosoma equiperdum*, however, caused the appearance in the serum of an autolysin which, like the lysin of paroxysmal haemoglobinurics, acted *in vitro* only after preliminary chilling of the mixture of red corpuscles and serum. The haemoglobinuric immune body whose properties have been described above is clearly distinct from the isolysins referred to previously, as is shown by the fact that the serum of the haemoglobinuric patient investigated by Grafe and Graham totally lacked isolytic action and the patient's red corpuscles were quite insensitive to isolytic sera. Injections of horse serum (Glaessner and Pick) and of cholesterin (Pringsheim) and peptone (Nolf) have been found to abolish the haemoglobinuric attacks, temporarily at least; but it is not clear how these bodies act.

Auxilytic and Antilytic Effects of Serum.

Serum has been found to influence the action of certain haemolytic bodies in varying degrees. This effect of serum clearly must depend upon a number of components. Thus, the haemolytic action of alcoholic extracts of autolysed tissues and that of oleic acid are inhibited by serum. In the case of organ extracts, Cruickshank found that the sera of different individuals showed variations in inhibitory power. Such action of the serum is, in part at least, due to the protein content, since albumin has the capacity for combining with acids, soaps, and lipoid substances. Again, serum possesses to a variable degree the property of aiding or inhibiting haemolysis due to cobra venom. Calmette, Massol and Breton drew attention to the action of the heated (58° C.) serum of tubercular patients in producing haemolysis of horse's red blood corpuscles along with cobra venom. They found the reaction present in 76 per cent. of cases of early phthisis. Similarly, in the case of twelve nursing women the whey of whose milk, after heating at 58° C. for half an hour, caused haemolysis along with cobra venom, nine reacted to tuberculin ; whereas of twelve women whose milk did not give the venom reaction only one reacted positively with tuberculin. Accordingly, the venom reaction appeared to afford a valuable means of diagnosing tubercular affections. V. Szaboki obtained a positive reaction with the serum of 92 per cent. of cases of phthisis and regarded the method as of value in diagnosing the disease at an early stage. Eitner and Stoerk, on the other hand, found the reaction negative in cases of lupus, although they obtained about 50 per cent. of positive results in phthisis. Unfortunately the results of other workers have been less constant and have shown that the serum may possess this property in other conditions. Bauer and Lehndorff obtained constantly a positive result with the serum of the retroplacental blood-clot at parturition; they also found that in cases of severe illness of almost any description a positive reaction was obtained more frequently than in health. Beyer obtained a positive result in all of eight cases of delirium tremens and in all of four cases of hepatic cirrhosis, as well as in 81 per cent. of acute infections (typhoid fever, pneumonia). The lytic action of the serum for venomized horse's blood has been recently investigated in carcinoma by v. Graff and v. Zubrzycki, who came to the following conclusions: (1) the serum of cases of carcinoma can haemolyse venomized corpuscles in over 70 per cent. of cases ; (2) only 10 per cent. of normal sera and of sera in other diseases react positively; (3) a positive result is obtained in cases of carcinoma in women who have been operated on years before and who have remained free from recurrence; (4) in pregnancy after the end of the third month the serum reacts positively; (5) after pregnancy the reaction remains positive till three weeks *post partum*. The results in pregnancy are in agreement with Römer's observations; he considers also that the haemolytic reaction runs parallel with the increased content of the serum in lipoids (Neumann and Hermann). Watson (unpublished results) tested the action of heated human serum along with cobra venom on ox blood in

a large series of cases of disease, including general paralysis, epileptic insanity, melancholia, diabetes, nephritis, &c. In one of the few cases in which the serum had a very marked lytic action on the venomized corpuscles—an advanced case of general paralysis—the post-mortem examination showed no lesions except those associated with the affection of the central nervous system; there was no tubercular infection and no tumour. H. G. and A. S. Grünbaum investigated the effect of heated human serum on the haemolysis of guinea-pig's red blood corpuscles along with cobra venom and fresh guinea-pig's serum. They found that with serum from cases of sarcoma and acute inflammatory conditions (pneumonia, appendicitis, tubercular peritonitis) haemolysis rapidly occurred, whereas haemolysis was slow in the presence of serum from cases of syphilis, phthisis, leukaemia, and some other conditions. The power of aiding haemolysis was also increased in the serum as the result of injections of vaccines or of the presence of infective conditions at a stage corresponding with that of the negative phase in the opsonic reaction. Much and Holzmann, again, studied the effect of fresh human serum on the lytic action of cobra venom for human red corpuscles; these workers came to the conclusion that in cases of mental disease belonging to Kraepelin's types of dementia praecox and manic depressive insanity the serum possessed the property in a marked degree of inhibiting haemolysis. This 'psycho-reaction' was regarded as specific and diagnostic for these conditions; but later observers (Ross and others) have been unable to confirm these conclusions.

The results of different workers have been highly contradictory in many instances and the whole subject requires further investigation. It may be taken as proved that the power of serum to aid or to inhibit the haemolytic action of cobra venom is susceptible to marked variations under different conditions; but whether or not the alterations in these properties depend on certain metabolic changes of constant occurrence in given diseases is as yet uncertain. The persistence of the auxilytic property of sera in cases of malignant tumour for years after radical and successful operation is highly suggestive that the reaction may serve as the index of a certain malignant diathesis and merits further research. It is also quite unknown to the presence of what bodies these effects of the sera are due; there is no evidence that the inhibitory action of the serum on cobra-venom haemolysis is due to cholesterin or that the auxilytic effect is caused by any known substance, such as a lipoid like lecithin.

The inhibitory effect of serum on the haemolytic action of saponin has been investigated by Herz and Landsteiner, who in 180 cases of various diseases found increased antilytic power marked only in severe jaundice, as a result, it may be, of increased content in cholesterin. Other properties, such as the powerful thermolabile anticomplement which some human sera acquire on being kept for a considerable time (Browning and Mackenzie), have not yet been investigated from the point of view of clinical significance. Again, Ruffer and his co-workers found that serum possesses the property of inhibiting the haemolytic action of bile of the same species. This power of serum does not, however, appear to have been extensively investigated.

Wright, along with Kilner and Ross, has estimated the degree to which serum and urine can be diluted with water without causing lysis of red blood corpuscles introduced into the medium. In this way the salt content of the fluids is probably measured and an indication of the excretory capacity of the kidneys is obtained, which may be of practical value in determining the nature of albuminuria.

The Detection of Antigens and Antibodies by means of Complement Deviation.

The principle on which the reaction of complement deviation depends is as follows: When certain antigens (that is, bodies which when injected into an animal's tissues lead to the development of antibodies) are added to the corresponding antibodies in suitable proportions, the mixture possesses the property of absorbing complement. In practice, complement-containing serum is added to the mixture of antigen and antibody, and after allowing a suitable time for the reaction to occur—usually one to two hours at 37° C.—red blood corpuscles, sensitized by the addition of the homologous immune serum, are added. Such sensitized corpuscles, termed the haemolytic system, constitute the test for complement. If no haemolysis occurs, then the complement added at the first stage is no longer free or available to cause haemolysis; it is said to have been 'deviated'. In this way, if one possesses a known antigen of suitable character, it is possible to test for the presence of the corresponding antibody, say, in a patient's serum. A mixture is made of the antigen and the serum in question; if this mixture deviates complement, then the serum contains the corresponding antibody. If complement deviation fails to occur, then the serum does not contain an antibody corresponding with the antigen employed. In precisely similar fashion, the possession of a known antiserum enables one to test for the presence of the corresponding antigen. With regard to the practical performance of such tests, certain points must be borne in mind. In the first place, the reaction is not a qualitative one, but is strictly quantitative; fixed amounts of antiserum and of antigen must be employed, and the amount of complement added must be measured according to its haemolytic power for the test amount of sensitized corpuscles. Only in this way is it possible to overcome the numerous fallacies which beset such tests when carried out in a rough-and-ready fashion. With regard to the criterion of a positive reaction, the fact is of importance that, as a rule, the antigen and the antiserum each by itself has a certain degree of inhibitory effect on complement. A true deviation of complement reaction occurs only when the combination of antigen and antibody absorbs much more complement than the sum of the amounts inhibited by each component separately. A further factor which requires attention is the relative proportion existing between the amounts of antigen and antibody employed. If either constituent is present in excess of the optimum amount, then complement deviation may fail to occur. This abolition of the reaction when one of the components is in excess is termed the zone phenomenon. It is obvious that by

neglecting the possibility of a zone, failure to detect antigen or antibody may result. The complement-deviation reaction is specific in the sense expressed by Ehrlich; that is to say, the antibody which is developed in the serum of an animal as an immunity reaction to the introduction of antigen—foreign protein—into its tissues has a specific affinity for that antigen alone. With this conception of specificity it is comprehensible that allied species of animals or micro-organisms should contain antigens in common. Thus human serum and monkey's serum contain certain antigens in common, so that antihuman serum contains antibodies to monkey's serum, and, as a result, a mixture of monkey's serum along with antihuman serum deviates complement, although not to the same extent as the combination of human serum with the corresponding antibody. The property of deviating complement is possessed by a great number of antigens in combination with their corresponding antibodies; thus the various serum and tissue proteins and bacteria in general give rise to complement-deviating antibodies; but certain toxins, e.g. that of the diphtheria bacillus, along with the homologous antitoxins are said not to deviate complement. In most bacterial infections, if sufficiently generalized, complement-deviating antibodies are present in the serum at some stage, although the reaction is not employed for diagnostic purposes in many instances, because other immunity reactions can be more rapidly applied, e.g. agglutination of B. typhosus in enteric fever. Complement-deviating antibodies occur in the serum in enteric fever, cerebro-spinal meningitis (Mackenzie and Martin), and many other bacterial infections. Schwartz and McNeil have obtained very good results in chronic gonococcal infections, in which the method should prove of practical importance, as the diagnosis of such cases by isolation of the specific organism is frequently a very difficult matter. An attempt has been made to detect by this method antibodies in the serum in cases of infection with higher animal parasites, e.g. intestinal worms, employing as antigen watery or alcoholic extracts of the worms (Kurt Meyer). Barit, in contrast to Meyer, obtained no evidence of specific complement deviation in eleven cases of infection with tapeworms. In echinococcus infection complement deviation has been obtained by using the hydatid fluid along with the patient's serum. Thomsen and Magnussen obtained complement deviation with ten out of twelve cases of echinococcus infection; but in four of these the action of the serum was not greater than is occasionally met with in uninfected persons. Thus, the results in the case of infections with higher parasites have not been of much practical value. Di Cristina failed to obtain complement deviation with the sera of cases of kala azar, using as antigen cultures of the parasite or extracts of the spleen of children dead of the disease.

The delicacy of the complement-deviation reaction is in certain cases very great; with a potent antihuman serum it is possible to detect 0·00001 c.c. of human serum. Wilson has employed the method in the examination of the urine in cases of albuminuria and nephritis. He found that the albuminous substances present were, in great part at least, of the nature of human antigen, and the biological test was ten to a hundred times more delicate than the usual chemical

tests (nitric acid, boiling with the addition of acetic acid). Thus the reaction was obtained in some cases after albumin had disappeared as tested by the ordinary methods. Normal urine contained no deviating bodies, and an interesting fact which Wilson elicited was that in the case of certain normal individuals no albumin could be detected in the urine by such a delicate reaction, even after violent physical exercise or cold baths.

The most valuable practical application of complement deviation is the syphilis reaction of Wassermann, Neisser, and Bruck. This was originally supposed to be an antigen-antibody reaction, the antigen consisting of constituents of the Spirochaete pallida contained in a watery extract of the liver from a case of congenital syphilis rich in spirochaetes and the antibodies being present in the serum of patients infected with syphilis. The fact that alcoholic extracts of normal organs or certain lipoids, such as lecithin (from liver or heart), or mixtures of these bodies with cholesterin, can act as 'antigen', shows clearly that the reacting substance in the serum is not an antibody to the specific causative agent of syphilis. As the lipoid antigens are not antigens in the true sense of the word, i. e. do not on injection into animals give rise to complement-deviating antibodies, the reaction cannot be regarded as a true antigen-antibody effect at all; but must be considered in the meantime as an accidental phenomenon which has been discovered by a false analogy. The reaction is nevertheless very highly specific; thus, with the exception of syphilis and framboesia, only a very small number of other diseases give a positive reaction, viz. tuberous leprosy and, perhaps, sleeping sickness. Hence for practical purposes of diagnosis the test possesses very great value. It is only possible to touch shortly here on some of the newer facts composing the enormous additions to knowledge which have been made as a result of the Wassermann reaction. By means of this test it has been shown that syphilitic infection is present at periods when clinical manifestations are absent, thus indicating the necessity for further treatment. In cases of known syphilitic infection in the latent stage, with negatively reacting sera, the existence of disease has been shown by the procedure of 'provocative' treatment, i.e. soon after treatment insufficient to produce complete sterilization, e.g. a single injection of salvarsan, the serum may come to react positively again for a brief period (Gennerich). This result of provocative treatment affords a very valuable therapeutic indication, and also provides a means of diagnosis in similar cases in which a definite history of infection is lacking. The Wassermann reaction has further proved invaluable in the investigation of family histories. The presence of a positive reaction in certain members of families in association with diseases of doubtful aetiology in other members, where the patients themselves may or may not react positively at the time of examination, has indicated the causal relationship of syphilis to the diseases in question. Thus Kerr Love, along with Browning and Cruickshank, has demonstrated the syphilitic nature of certain cases of sporadic congenital deafness, and has brought forward strong evidence in favour of the view that congenital syphilis may be responsible for a much greater proportion of such

cases than has hitherto been supposed. Similarly, it has been proved that syphilitic infection is practically a constant factor in the production of paroxysmal haemoglobinuria *e frigore*. The investigation of families where the parents or certain members are syphilitic has shown that children apparently in good health may be really infected. An investigation of 120 out of 124 consecutive admissions, *other than general paralytics*, to Gartloch (Glasgow Parish) Asylum, by Gilmour,[5] has shown a positive Wassermann reaction with the serum of 18 per cent. of 72 female cases and 27 per cent. of 48 male cases, thus proving that, in this class of patients at least, syphilis is by far the most frequent condition associated with insanity. Observations on the occurrence of a positive reaction with the cerebro-spinal fluid in 'florid' syphilis indicate that a general infection of the central nervous system is much more frequent at that stage than has hitherto been supposed (Bergl). The researches of Candler, Gilmour, and others have shown that in certain rare cases of general paralysis a positive reaction with the cerebro-spinal fluid may afford the only evidence of the syphilitic nature of the case during life, while the serum persistently gives a negative reaction. Von Dungern has applied a procedure similar to the Wassermann reaction for the diagnosis of cancer, employing as antigen an alcoholic extract of tumour tissue or the alcohol-soluble constituents of an acetone extract of normal human red blood corpuscles, and he claims to have obtained reliable results (see also Lindenschatt); but this has not been confirmed (Rosenberg).

Complement deviation has also been widely investigated in connexion with tuberculosis. Wassermann and Bruck originally demonstrated in watery extracts of tubercular tissues the presence of antituberculin, which along with tuberculin led to complement deviation; but they failed to detect antibodies in the serum of tubercular subjects, except in advanced cases or in those who had been treated with tuberculin. Recent investigations by Möllers and others have tended to support the view that the presence of antibodies in the serum possesses no significance either from the point of view of prognosis or diagnosis. On the other hand, certain workers have obtained complement deviation in a large proportion of cases of tuberculosis, including lupus and surgical affections (Hammer). The varying character of the observations is in all probability due to differences in the methods of procedure, and the use of a suitable antigen may lead to more uniform results. It is especially true of investigations by means of complement deviation that there can be no short cut to reliable results, and the work of many observers has been carried out with insufficient attention to details of method, so that there is still in this department a wide field for accurate and painstaking research.

[5] I am indebted to Dr. Gilmour for these unpublished results.

Haemolytic Anaemias: Blackwater Fever.

Increased blood destruction occurs in a variety of conditions, viz. pernicious anaemia, congenital family icterus (Minkowski), haemolytic icterus (Hayem-Widal, Banti), paroxysmal haemoglobinuria, blackwater fever, and a number of other infections and intoxications accompanied by haemoglobinuria (see Miller), also possibly in some cases of leukaemia and in bronzed diabetes. The question which concerns us here is whether any of these conditions is due to the action of a haemolysin, and if so, what the nature of the lytic process is. Haemoglobinaemia and haemoglobinuria occur in only the minority of conditions in which extensive blood destruction is taking place. Haemoglobinaemia has been definitely observed in blackwater fever, paroxysmal haemoglobinuria, and cases of severe burning. In other diseases the occurrence of haemolysis is inferred from anaemia associated with the presence of deposits of iron in the organs—liver, kidney, spleen, and bone marrow—jaundice or excess of urobilin in the faeces and urine, and alterations in the erythroblastic elements of the bone marrow. The occurrence of haemoglobinuria (apart from a lesion in the urinary tract) and the detection of haemoglobinaemia, of course, afford positive evidence of lysaemia; but these conditions depend both on the amount of haemoglobin which is set free into the blood plasma and also on the rate at which the haemoglobin is liberated. As Pierce, Austin and Eisenbrey have shown, haemoglobin is not removed by the kidney till its concentration in the serum reaches a certain level (0·06 gramme per 1,000 grammes of body weight in the case of dogs); when the concentration is lower haemoglobinuria does not occur. The liver, however, and possibly other tissues take up haemoglobin as soon as mere traces are present in the serum. Even when more haemoglobin is present than the liver can deal with, so that haemoglobinuria results, the amount which is excreted by the kidney is only a half to a fifth of the amount disposed of by the liver and tissues. The haemoglobin taken up by the liver is converted into bile pigments. If large amounts of haemoglobin are transformed in this way the bile capillaries are unable to remove the products sufficiently rapidly, so that cholaemia and choluria result; but a very considerable amount of haemolysis may occur without overtaxing the excretory mechanism of the liver. It is clear, therefore, that extensive and long-continued haemolysis may take place without haemoglobinaemia being detectable and without haemoglobinuria occurring. Thus, in cases of pernicious anaemia it is only exceptionally that haemoglobin can be found in the plasma in greater abundance than may occur, as an artefact no doubt, when normal specimens are examined in a similar fashion (addition of potassium oxalate to the blood and separation of the plasma by the centrifuge).

The production of lysaemia may be due to lytic agents of different types: (1) bacterial, protozoal, and metazoal toxins; (2) haemolysins analogous to the immune haemolysin, consisting of immune body and complement; (3) haemolytic

bodies elaborated from the tissues by the action of toxic agents. These classes of lysins will be considered briefly.

Haemolytic toxins. Such bodies may be formed in the alimentary canal and thence absorbed into the circulation (Hunter). Thus Tallqvist has suggested that bothriocephalus anaemia is due to the absorption of haemolytic lipoids which are set free from dead and macerated worms in the intestine. Lüdke and Fejes consider that B. coli in the intestine produces haemotoxins which are of the nature of fatty acids, and that strains of this organism obtained from cases of pernicious anaemia are more actively haemolytic than those from normal individuals. These workers claim to have produced experimentally the blood picture of pernicious anaemia in animals by the administration of the coli haemotoxin and to have cured the anaemia by injections of antiserum. In this connexion it is to be noted, however, that other observers (Kayser) have been unable to obtain an active haemolysin for human blood from B. coli. Haemoglobinuria has been observed in streptococcus septicaemia (Rostoski). McLeod in his study on the haemolysin production of streptococci found that the type of this organism inhabiting the bowel, including strains from cases of pernicious anaemia, did not form haemolysin. The fact that it is impossible to obtain an antiserum to a bacterial haemotoxin such as streptolysin is highly suggestive as explaining why a condition like pernicious anaemia, if due to some infection, takes a progressively unfavourable course. In tertian malaria, at certain stages of its cycle, Simpson has found haemolysins in the serum (see also Brem).

Complex serum haemolysins. As has been mentioned already, the only condition in which an autolysin of this type has been constantly demonstrated is paroxysmal haemoglobinuria. Carraciolo states that he has found a thermolabile haemolysin in the serum of patients infected with anchylostomiasis. The existence of a lytic agent which is acting in the body cannot be excluded, however, on account of failure to demonstrate its operation *in vitro*, since Muir and McNee have produced marked lysaemia by the injection of an amount of haemolytic immune body which was unable to produce lysis in the test-tube.

Haemolysins elaborated from the tissues. The production of haemolytic substances of fatty acid type, similar to the lytic products which develop from fats and lipoids when the liver undergoes aseptic autolysis, has been advanced as an explanation of the haemolysis which follows the administration of toluylenediamine, since this substance does not in itself act as a lytic agent for red blood corpuscles *in vitro* (Joannovics and Pick, Maidorn). Changes in the liver which are histologically characterized as 'fatty', and which are due mainly to the liberation of fat from the intimate combination with protein in which it exists under normal conditions, are common in the diseases under discussion. It is possible, therefore, that the fatty liver itself acts as the source of haemolysin. This conception of the formation of haemotoxin from the tissues as a secondary consequence of damage by an infective agent or its toxins appears to be worthy of much more extended investigation. But conclusions regarding *intra vitam* processes based on the examinations of tissue extracts obtained by powerful

extractive agents like alcohol and ether must be accepted with reserve. These reagents tend to split up protein-fat complexes and thus yield bodies which have no existence as such in the living tissues.

With regard to the action of lytic agents in general, it is to be noted that corpuscles which have been damaged to an extent short of undergoing lysis may be rendered susceptible to phagocytosis, which is apparently the normal process of disposal of effete red cells in the body. Haemolytic immune serum in amounts insufficient to cause lysis has been shown to act in this way, by 'opsonizing' the red corpuscles. Accordingly, a haemolytic agent in a low concentration may merely have the effect of exaggerating the normal process of blood destruction. That a healthy animal does not readily depart from its usual mechanism of blood disposal has been shown by Boycott and Douglas; thus, when they produced a haemic plethora by repeated injections of blood of the same species into rabbits, the excess was disposed of extremely rapidly by the spleen. In these experiments no haemoglobinaemia developed, and there was no deposition of excess of iron-containing pigment in the liver and kidney. Instead of damage to the red corpuscles as the result of a toxic agent being the factor predisposing to phagocytosis and haemolysis, there may be the production of red cells by the marrow, which are abnormally fragile. Such abnormal fragility of the red cells, as tested by their diminished resistance to hypotonic salt solution and to saponin (Pel, Roth), has been held responsible for the causation of haemolytic icterus. On the other hand, the phagocytic property of a tissue or its power of producing haemolysin may undergo an increase and lead to excessive destruction of normal red cells. Some such increased activity of the spleen would appear to be an important factor in the cases of haemolytic splenomegaly described by Banti, in which cure is effected by splenectomy. In the case of experimental trypanosonic anaemia Boycott and Price-Jones have found that the red cells are destroyed by phagocytosis in the lymph-glands, the iron of the destroyed haemoglobin being stored in the liver and spleen. No reason for the blood destruction could be discovered.

How complex the conditions are which underlie blood destruction may be illustrated by a further reference to blackwater fever; in this disease, in which, as Christophers and Bentley have shown, a process of lysaemia leads to most rapid and extensive blood destruction, no haemolysin has been demonstrated (Barratt and Yorke), and there is no explanation which brings into harmony the main facts, viz. that (1) malarial infection is practically an invariable precursor, but is frequently latent at the time of an attack of blackwater; (2) a very small amount of quinine may induce an attack, but after the attack large amounts of quinine can be tolerated; (3) attacks may supervene in cases which have never been treated with quinine; (4) drugs, such as antipyrine, which are not antiparasitic, may induce an attack. It remains to be seen whether the presence of the parasite observed in the blood from certain cases by Leishman will, by establishing the true causative agent, lead to an elucidation of these points. Thus, the whole problem of diseases characterized by increased

blood destruction is a very difficult one, and the present state of knowledge permits no more than an indication of the possibilities with regard to the participation of haemolytic agents in the production of these affections.

REFERENCES.

The references given here are mainly to recent works which contain full lists of older publications.

The Mode of Action of Haemolysins.

Ascoli, *Zeitschr. f. Chem. u. Industrie d. Kolloide*, Dresden, 1909, v. 293.
Bang, *Chemie und Biochemie der Lipoide*, Wiesbaden, 1911.
Bordet, *Studies in Immunity* (Engl. translation), Lond., 1909. (Serum-haemolysis.)
Browning and Mackie, *Zeitschr. f. Immunitätsforschung*, Jena, 1913, Teil 1, xvii. 1.
Cruickshank and Mackie, *Biochem. Zeitschr.*, Berlin, 1912, xlii. 414.
Ehrlich, *Studies in Immunity* (Engl. translation), Lond., 1909.
Fischer, *Zeitschr. f. Chem. u. Industrie d. Kolloide*, Dresden, 1909, v. 146. (Physical chemistry of haemolysis.)
Hamburger, *Osmotischer Druck und Ionenlehre*, I, 1902. (Ditto.)
Höber, *Die physikalische Chemie der Zelle und der Gewebe*, Leipzig, 1911. (Ditto.)
v. Liebermann and v. Fenyvessy, *Zeitschr. f. Immunitätsforschung*, Jena, 1912, Teil 1, xiii. 695.
McLeod, *Journ. of Path. and Bact.*, Camb., 1911–12, xvi. 321.
McNeil, *Journ. of Path. and Bact.*, Camb., 1911, xv. 56.
Manwaring, *Zeitschr. f. Immunitätsforschung*, Jena, 1909, Teil 1, iii. 309.
Mees, *La Cellule*, Lierre et Louvain, 1912, xxvii. 7. (Immunizing constituents of red corpuscles.)
Metchnikoff, in *Kolle-Wassermann's Handbuch der pathogenen Mikroorganismen*, 2. Aufl., Jena, 1913, ii. 655.
Moore, *Brit. Med. Journ.*, 1909, ii. 684.
Moore and Roaf, *Biochem. Journ.*, Liverpool, 1908, iii. 55.
Muir, *Studies in Immunity*, Oxford, 1909. (Serum-haemolysis.)
Muir and McNee, *Journ. of Path. and Bact.*, Camb., 1911–12, xvi. 410, and xvii. 92.
Müller, *Cent. f. Bakt.*, Jena, 1911, Orig. I, lvii. 577.
Nolf, 'Hémolyse' in *Dictionnaire de Physiologie*, Paris, 1908.
Přibram and Russ, in *Kraus und Levaditi's Handbuch der Technik und Methodik der Immunitätsforschung*, Jena, 1908, i. 202. (Haemotoxins.)
Roaf, *Quart. Journ. Exper. Physiol.*, Lond., 1912, v. 131.
Rywosch, *Pflüger's Arch. f. die ges. Physiol.*, Bonn, 1907, cxvi. 229.

Alterations in the Resistance of Red Corpuscles to Haemolytic Agents.

v. Graff and v. Zubrzycki, *Arch. f. Gynäkol.*, 1912, xcvi. 732.
Heuberger and Stepp, *Deutsch. Arch. f. klin. Med.*, Leipzig, 1912, cvi. 525.
Hirschl and Pötzl, *Wien. klin. Woch.*, 1909, 949.
Kraus, Graff and Ranzi, *Wien. klin. Woch.*, 1911, 1003.
Kraus, Pötzl, Ranzi and Ehrlich, *Wien. klin. Woch.*, 1909, xxii. 1027.
Maliwa, *Deutsch. med. Woch.*, 1913, xxxix. 154.
Massaglia and Tarabini, *Gazz. d. osp. e delle clin.*, Milano, 1908, xxix. 778.
Oczesalki and Sterling, *Zeitschr. f. Immunitätsforschung*, II. Ref., 1912, 547.
Pel, *Deutsch. Arch. f. klin. Med.*, 1912, cvi. 239.
Port, *ibid.*, 1910, xcix. 259.
Roth, *Deutsch. Arch. f. klin. Med.*, 1912, cvi. 137.
Rous, *Journ. of Exper. Med.*, New York, 1909, xi. 763.

Sättler, *Fol. Haematol. Arch.*, 1910, ix. 216.
Schwartz, *New York Med. Journ.*, 1912, xcv. 23.
Slingenberg, *Arch. f. Gynäkol.*, 1911, xciii. 87.
Snapper, *Biochem. Zeitschr.*, Berlin, 1912, xliii. 256.
v. Stejskal, *Wien. klin. Woch.*, 1909, 1701.
Stone and Schottstaedt, *Arch. of Int. Med.*, 1912, x. 8.
Weil, *Journ. of Infect. Dis.*, 1909, vi. 688.

Serum-Complement.

Backman and Jacobaeus, *Compt. rend. Soc. de Biol.*, Paris, 1909, lxvii. 415.
Breton, Massol et Minet, *ibid.*, 576.
Eliasberg, *Deutsch. med. Woch.*, 1911, xxxvii. 302.
Engel, *ibid.*, 1910, xxxvi. 986.
Findlay, Fua and Noeggerath, *Jahrb. f. Kinderheilk.*, 1909, lxx. 732.
Fornario, cited by Friedberger in *Die Anaphylaxie, Fortschritte d. deutsch. Klinik*, Berlin, 1911, 619.
Marshall, *Journ. of Exper. Med.*, New York, 1905, vi. 347.
Popoff, *Zeitschr. f. Immunitätsforschung*, Jena, 1. Teil, Orig., 1912, xiv. 218.
Ssirensky, *ibid.*, Ref., 1912, iv. 313.
Ssirensky and Nawrozky, *ibid.*, 312.

Natural Immune Bodies in Serum.

Aschenheim, *Cent. f. Bakt.*, Orig. I, 1909, xlix. 124.
Gewin, *Zeitschr. f. Immunitätsforschung*, Jena, 1. Teil, Orig., 1909, i. 613.
Kelling, *Arch. f. Verdauungs-Krankh.*, 1912, xviii. 164, 329.
Kraus, *Zeitschr. f. Immunitätsforsch.*, Ref., 1912, iv. 523.
Wilson, *Brit. Med. Journ.*, 1909, ii. 866.

Haemolysins in Cerebro-spinal Fluid, Exudates, &c.

Kafka, *Zeitschr. f. d. ges. Neurol.*, Orig., 1912, ix. 132.
Lane-Claypon, *Journ. of Path. and Bact.*, Camb., 1908, xiii. 34.
Mijashita, *Klin. Monatsbl. f. Augenheilk.*, Beilageheft zum xlviii. Jahrg.
Mutermilch and Hertz, *Zeitschr. f. Immunitätsforschung*, Ref., 1912, iv. 547.
Noeggerath, *Jahrb. f. Kinderheilk.*, 1909, lxx. 701.
Tschirkowsky, *Klin. Monatsbl. f. Augenheilk.*, 1912, l. 145.

Isolysins.

Ascoli, *Münch. med. Woch.*, 1901, 1239.
Bürger, *Zeitschr. f. exper. Path. u. Ther.*, Berlin, 1912, x. 191.
Crile, *Journ. of Amer. Med. Assoc.*, 1908, li. 2036; *Haemorrhage and Transfusion*, New York, 1909.
v. Dungern and Hirschfeld, *Zeitschr. f. Immunitätsforschung*, Jena, 1. Teil, Orig., 1910, iv. 531, vi. 283.
Gorham and Lisser, *Amer. Journ. of Med. Sci.*, 1912, cxliv. 103.
Gräfe and Graham, *Münch. med. Woch.*, 1911, lviii. 2257.
Landsteiner and Leiner, *Cent. f. Bakt.*, Jena, Orig. I, 1905, xxxviii. 548.
Moreschi, *Berl. klin. Woch.*, 1903, 973.
Moss, *Fol. Serol.*, 1910, v. 267.
Schultz, *Berl. klin. Woch.*, 1910, xlvii. 1407, 1457, and 1911, xlviii. 934.
Todd and White, *Proc. Roy. Soc.*, Lond., B, 1912, lxxxiv. 255.

Autolysins.

Bergh, *Berl. klin. Woch.*, 1909, xlvi. 1251.
Browning and Watson, *Journ. of Path. and Bact.*, Camb., 1912, xvii. 117.
Cooke, *Amer. Journ. Med. Sci.*, 1912, cxliv. 203.

Donath and Landsteiner, *Münch. med. Woch.*, 1904, li. 1590; *Zeitschr. f. klin. Med.*, Berlin, 1906, lviii. 173; *Cent. f. Bakt.*, Jena, Orig. I, 1908, xlv. 205.
Dudgeon, *Proc. Roy. Soc.*, Lond., B, 1908, lxxx. 531.
Eason, *Journ. of Path. and Bact.*, Camb., 1906, xi. 167.
Ehrlich, *Farbenanalytische Untersuchungen*, Berlin, 1891.
Glaessner and Pick, *Zeitschr. f. exper. Path. u. Ther.*, Berlin, 1911, ix. 581.
Meyer and Emmerich, *Deutsch. Arch. f. klin. Med.*, 1909, xcvi. 287; *Münch. med. Woch.*, 1908, 2153.
Moro, Noda and Benjamin, *Münch. med. Woch.*, 1909, lvi. 545.
Moss, *Johns Hopkins Hosp. Bull.*, Baltimore, 1911, xxii. 238.
Nolf, *Bull. et Mém. Soc. méd. d. Hôp. de Paris*, 1909, 3e sér., xxviii. 657.
Pringsheim, *Münch. med. Woch.*, 1912, lix. 1757.
Simpson, *Ann. of Trop. Med. and Parasitol.*, 1912, vi. 231; 1910–11, iv. 313.
Vogt, *Münch. med. Woch.*, 1910, 15.
Widal and Rostaine, *Compt. rend. Soc. de Biol.*, Paris, 1905, lviii. 321; 1906, lix. 406.

Auxilytic and Antilytic Effects of Serum.

Bauer and Lehndorff, *Wien. med. Woch.*, 1909, 1615.
Beyer, *Münch. med. Woch.*, 1909, 2206.
Browning and McKenzie, *Journ. of Path. and Bact.*, Camb., 1909, xiii, 325.
Calmette, Massol and Breton, *Compt. rend. Soc. de Biol.*, Paris, 1908, lxv. 648.
Eitner and Stoerk, *Wien. klin. Woch.*, 1909, 808.
v. Graff and v. Zubrzycki, *Münch. med. Woch.*, 1912, 574.
Grünbaum, H. G. and A. S., *Journ. of Path. and Bact.*, Camb., 1912, xvii. 82, 126.
Hermann and Neumann, *Biochem. Zeitschr.*, Berlin, 1912, xliii. 47.
Herz and Landsteiner, *Med. Klinik*, 1910, 1062.
Much and Holzmann, *Münch. med. Woch.*, 1909, 1001.
Römer, *Zeitschr. f. Geburtsh. u. Gynäkol.*, 1912, lxxi. 350.
Ross, *Journ. of Ment. Sci.*, Lond., 1911, lvii. 134.
Ruffer, *Brit. Med. Journ.*, Lond., 1904, ii. 581.
Ruffer and Crendiropoulo, *Journ. of Path. and Bact.*, 1904, ix. 278.
Wright and Kilner, *Lancet*, 1904, i. 921.
Wright and Ross, *ibid.*, 1905, ii. 1164.

Complement Deviation.

Barit, *Über den biologischen Nachweis von Parasiten*, Dissertation, Königsberg, 1912.
Bergl, *Vortrag gehalten auf der Versammlung des deutschen Vereins für Psychiatrie*, Kiel, 1912.
Browning and McKenzie, *Recent Advances in the Diagnosis and Treatment of Syphilis*, Lond., 1911.
Browning and Watson, *International Clinics*, 1913.
Candler, *Proc. Roy. Soc. of Med.*, 1912, v. Sect. 1, 169.
Dean, *Brit. Med. Journ.*, 1910, ii. 1516.
Di Cristina, *Pathologica*, Genova, 1912, iv. 409.
v. Dungern, *Münch. med. Woch.*, 1912, lix. 65, 1093.
Gennerich, *Die Praxis der Salvarsanbehandlung*, Berlin, 1912.
Hammer, *Münch. med. Woch.*, 1912, lix. 1750.
Kerr Love, *Glasgow Med. Journ.*, 1913.
Lindenschatt, *Deutsch. med. Woch.*, 1912, xxxviii. 2175.
Mackenzie and Martin, *Journ. of Path. and Bact.*, Camb., 1908, xii. 539.
Meyer, *Zeitschr. f. Immunitätsforschung*, Jena, Teil 1, 1910, vii. 732; 1911, ix. 530; 1912 xiv. 303.
Möllers, *Deutsch. med. Woch.*, 1912, xxxviii. 745.
Muir and Martin; see Muir, *Studies in Immunity.*

Rosenberg, *Deutsch. med. Woch.*, 1912, xxxviii. 1225.
Schwartz and McNeil, *Amer. Journ. of Med. Sci.*, 1911, cxli. 693.
Thomsen and Magnussen, *Deutsch. med. Woch.*, 1912, xxxviii. 1183.

Haemolytic Anaemias: Blackwater Fever.

Banti, *Lo Sperimentale*, 1912, lxvi. 91.
Barratt and Yorke, *Ann. of Trop. Med. and Parasitol.*, 1909–10, iii. 1.
Boycott and Douglas, *Journ. of Path. and Bact.*, Camb., 1909, xiii. 256.
Boycott and Price-Jones, *ibid.*, 1912–13, xvii. 347.
Brem, *Arch. of Intern. Med.*, 1912, ix. 129.
Carraciolo, *La Clin. Med. Ital.*, 1911, l. 65.
Christophers and Bentley, *Scientific Memoirs by Officers of the Medical and Sanitary Departments of the Government of India*, 1908, No. xxxv.
Kayser, *Zeitschr. f. Hyg.*, 1903, xlii. 118.
Labbé and Bith, *Bulletins et Mém. de la Soc. méd. des Hôp. de Paris*, 1912, xxviii. 119. (Bronzed diabetes.)
Leishman, *Journ. R. A. M. C.*, 1912, xviii. 493; *Trans. Soc. Trop. Med. and Hyg.*, 1912, vi. 1.
Lüdke and Fejes, *Verh. d. Kongr. f. inn. Med.*, 1912, xxix. 335.
Maidorn, *Biochem. Zeitschr.*, Berlin, 1912, xlv. 328.
McLeod, *Journ. of Path. and Bact.*, Camb., 1911–12, xvi. 321.
Miller, *Berl. klin. Woch.*, 1912, xlviii. 1921.
Muir and McNee, *Journ. of Path. and Bact.*, Camb., 1911–12, xvi. 410; 1912–13, xvii. 92.
Pierce, Austin and Eisenbrey, *Journ. Exper. Med.*, New York, 1912, xvi. 375.
Rostoski, *Festschrift f. von Rindfleisch*, Leipzig, 1907 (cited in *Münch. med. Woch.*, 1909, 408).
Roth, *Deutsch. Arch. f. klin. Med.*, 1912, cvi. 137.
Tallqvist, *Zeitschr. f. klin. Med.*, Berlin, 1907, lxi. 427.

ON AURICULAR FIBRILLATION

By A. M. GOSSAGE and J. A. BRAXTON HICKS

The recognition that fibrillation of the auricles occurs not unfrequently in human beings is the most important advance made during recent years in the study of the clinical aspects of disease of the circulatory organs. While it is possible to induce auricular fibrillation in the exposed hearts of animals by such means as powerful stimuli applied to the auricle, the study of such exposed hearts has not so far afforded much help towards understanding why the unexposed auricle in a human being should start fibrillating, and the exact causation of the condition is still unknown. In future attempts to find a solution of this problem all the available facts must be reviewed, and it is the purpose of this paper to indicate some points which will require consideration.

Fibrillation always starts suddenly, and when once started it is often permanent, but sometimes there are attacks of auricular fibrillation of varying duration before the condition becomes finally permanent. An example of this is afforded by the following case:

Case I. T. L., a grocer's assistant, aged 58, had for two years suffered from attacks of agonizing pain through the right side of the chest and down the inner side of the right arm. The pain usually came on after exertion or on going out into the cold air, and lasted seven or eight hours. Towards the end of the attack he frequently became dizzy and sometimes lost consciousness. The attacks were getting more severe and more frequent, coming on recently every

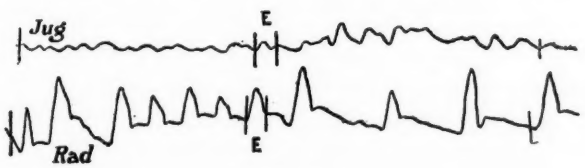


Fig. 1.

other day. On examination the heart was found to be dilated and its rhythm very irregular; occasionally a systolic murmur could be heard at the apex and also one over the aorta. No evidence of an intrathoracic aneurysm could be obtained. There was tenderness over the right side of the chest and down the inner side of the right arm and forearm (i. e. in the area of distribution of his pain). A tracing (Fig. 1) taken at this time shows the characteristics of auricular fibrillation, a complete irregularity of the heart and a purely systolic venous pulse. His feca was cyanosed and there was very considerable dyspnoea on

exertion, but there was no dropsy and no enlargement of the liver could be made out. The man returned to the hospital the next week looking an entirely different person: the cyanosis had disappeared and he moved about with ease and comfort. His attacks of pain were less frequent and less severe, and those that had occurred had been to some extent relieved by nitro-glycerine. The rhythm of the heart was now perfectly regular (Fig. 2), and the jugular pulse normal, showing a well-marked presystolic wave *a* before the systolic wave *c*. This patient remained in fair health with a normal action of the heart for about eighteen months, when he was again suddenly attacked with fibrillation of the auricles, and he died two months later of heart failure, the rhythm being constantly that of fibrillation (Fig. 3). After death the left ventricle was found to be dilated and hypertrophied; there was stenosis of the aortic valve, some atheroma of the aorta, and to a slight extent of the coronaries.

In speculating on the possible etiology of auricular fibrillation two views suggest themselves. According to the first the fibrillation would be due to some morbid condition of the muscle fibres, the actual ultimate stimulus which starts it being some sudden strain or the cumulative effect of prolonged overwork, as might be imagined to occur in valvular disease. One naturally favours this view as the condition usually follows an illness where there has been disease of the cardiac valves or evident muscular impairment. The other view would suppose that the fibrillation is due to some extrinsic stimulus (e.g. an altered chemical constitution of the blood) which, while more likely to influence an already diseased organ, might yet, if sufficiently strong, cause fibrillation in a heart that was previously healthy. There are, of course, obvious arguments to be brought against this view. To begin with, it presupposes an hypothetical something outside the heart, of the existence of which there is no direct evidence, although it is true that a drug—digitalis—will sometimes induce fibrillation of the auricles; but, as a rule, this only lasts for a short time. It is, again, very difficult from purely clinical and anamnestic evidence to be sure that a particular heart was healthy before the onset of the fibrillation. Although this second explanation seems at first sight improbable, yet it requires to be considered, and there are certain facts which tell in its favour. The development of auricular fibrillation is sudden, though there has usually been some sign of cardiac impairment beforehand, such as valvular disease or dyspnoea on exertion. In some cases, however, we are quite unable to get any evidence of the heart being otherwise than sound before the onset of the fibrillation, even where, as in Case III, the patient has been under more or less close observation for a fairly long period beforehand. The following cases afford examples of this type:

Case II. A brewer, aged 59, who was a big heavy man, 5 feet 11 inches high and weighing 17 stone, had been in perfect health and able to do heavy work up to a week before he came to the hospital. He was then suddenly attacked with cough and dyspnoea, so severe that he could hardly get about. He had had no previous serious illness, but had been accustomed to drink large quantities of beer until a few months before the onset of his complaint. On examination he was cyanosed, especially on lying down, and had a great deal of dyspnoea; the chest was rigid but the lungs were normal; the heart rhythm was rapid and irregular, and there was no bruit; the liver was enlarged, and there was tenderness over it; there was no dropsy. The tracing (Fig. 4) shows typical

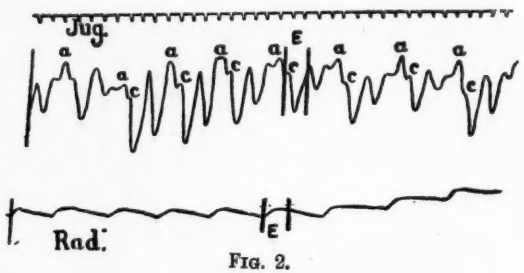


FIG. 2.

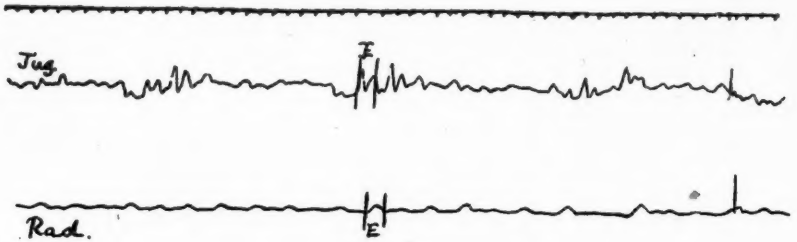


FIG. 3.



FIG. 4.

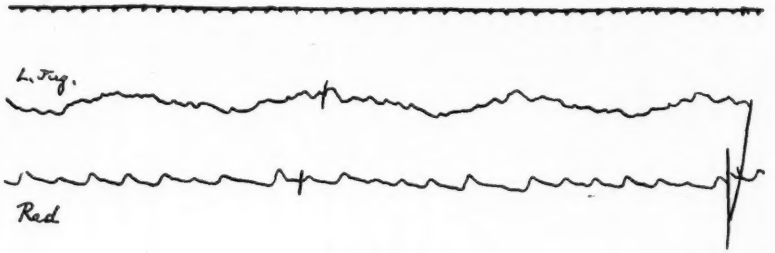


FIG. 5.

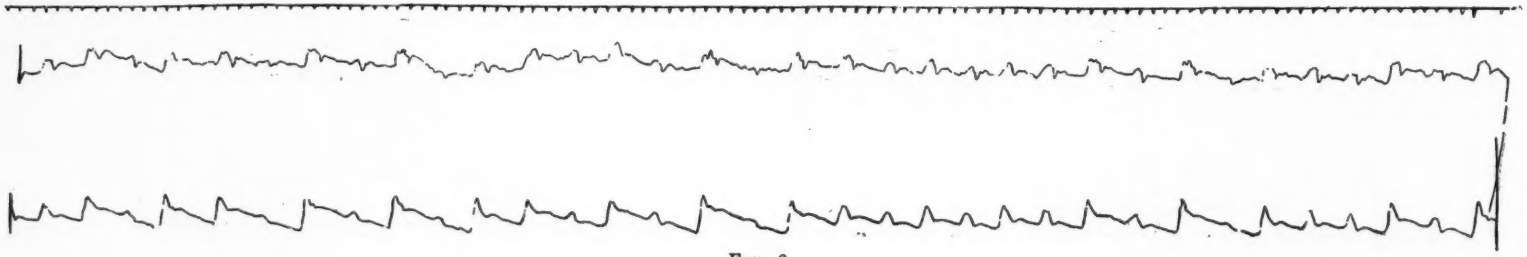


FIG. 6.

auricular fibrillation with a purely systolic venous pulse. This man was never seen again, so that his subsequent history is unknown.

Case III. G. S., a street-sweeper, who is now 74 years old, had been a regular attendant in the out-patient department for five years, suffering with osteoarthritis of the right hip. His vessels were decidedly degenerate, but the heart was apparently normal on physical examination, and he had no discomfort or dyspnoea on exertion. At the end of 1910 he was suddenly attacked with dyspnoea, pain in the left side, and general feeling of illness. He came to the hospital ten days later, when the heart was found to be considerably dilated and to be persistently irregular, showing the characteristic tracings of auricular fibrillation (Fig. 5). Rest in bed and treatment with digitalis improved his condition considerably, and he has now remained in fair comfort for fourteen months provided he does not overexert himself. During this time he has almost constantly taken 10 minims of tincture of digitalis three times a day, any cessation of the drug for even a day or two being followed by increased rapidity of pulse and uncomfortable dyspnoea on even slight exertion. Since the first onset of the auricular fibrillation the condition has been present on every occasion on which he has been examined, and since these occasions have been frequent the condition is evidently permanent (Fig. 5).

With regard to these two cases it is, of course, impossible to assert that the hearts were normal before the onset of the fibrillation of the auricles. In one case there was abuse of alcohol, a well-known cardiac poison, and in the other well-marked vascular degeneration which possibly implicated the coronaries. It is noticeable, however, that in neither case were there any symptoms referable to cardiac impairment until the sudden onset of the fibrillation.

A more important case in this connexion is the following:

Case IV. G. B., a short, muscular, well-built man, aged 23, was employed as a barrow-minder in Covent Garden, an easy occupation involving no strain and affording him, according to the police, a comfortable living. His previous health had been good, and he had never had rheumatism or syphilis. He was married, and his wife had had three healthy children and no miscarriages. With the exception of a slight cough for a week he was perfectly well until October 24, 1909, when, after a fit of coughing, he was attacked with pain over the heart and dyspnoea. A few hours later he was admitted into the Westminster Hospital and was seen and examined by one of us. He had some slight cyanosis and considerable dyspnoea; the heart rhythm was very irregular and characteristic of auricular fibrillation (Fig. 6); the heart was only slightly enlarged, the apex beat being in the fifth intercostal space half an inch internal to the nipple line.

With rest and the administration of 5 minims of tincture of strophanthus every four hours the patient improved, but on leaving the hospital the dyspnoea soon got worse and he suffered with pain and palpitation. He was readmitted into the hospital on January 29, 1910, and again on May 10, and on each occasion improved rapidly with rest and treatment. In May it was noted that the heart had increased in size, the apex beat being in the fifth space an inch external to the nipple. He was again admitted on September 13, 1910, with pain and dyspnoea and some bronchitis. On this as on all the previous occasions the characteristic irregularity of the heart rhythm was constantly present. On discharge he attended regularly in the out-patient department, and on November 16 the apex beat was noted to be in the sixth space, 2 inches external to the nipple. As there was a tendency for the return of the dyspnoea and pain he was given 10 minims of tincture of digitalis three times a day, and after a week was much better. The pulse rate was reduced to 43 per minute, the great reduction being

only apparent and due to a bigeminal action of the heart, the rate of which was really 86 (vide Fig. 7). The dose of the digitalis was reduced to 7½ minims t. d. s., and this was continued up to his death in the following May. During these four months the man felt better than he had done since the start of his illness and had no return of the bronchitis. The heart rhythm continued irregular and characteristic of auricular fibrillation, but was not rapid, and he was able to return to work and to do his business with comfort except for a little pain over the heart on two occasions. Throughout his illness he had never had any dropsy and the liver was never felt: no bruit was ever heard. On May 14, 1911, he ran across the road after a friend and fell down dead.

At the post-mortem examination, twenty hours after death, the body was noted as being of good muscular development. The heart, 20 oz., was taken out as a whole and hardened in formalin, but at the time it was noted that there were no valvular lesions, that the left ventricle was hypertrophied and dilated, and that there were no macroscopic changes in the musculature of the other cavities. The arteries were quite healthy. There were some adhesions of the left pleura, and both lungs were congested and tough, i.e. cardiac. The intestines were congested and the liver darker than normal, but not nutmeg. The spleen was firm and the kidneys cardiac, i. e. engorged and firm on section. No evidence of syphilis could be found.

Microscopic examination of the cardiac muscle. Blocks were taken from the superior vena cava, the auricles, the ventricles, and the region containing the bundle of His, embedded in paraffin and sections cut; numerous sections from each part were examined, while the blocks containing the bundle of His were cut serially and every thirtieth section examined. In no section could anything abnormal be found; the muscle fibres looked healthy, there were no collections of leucocytes and no increase of fibrous tissue. Death had probably been due to fibrillation of the ventricles.

This case, of course, does not establish the proposition that fibrillation of the auricles may come on in a previously healthy heart, but it certainly suggests that this is possible. Such changes as were found in the heart might very well have been a consequence and not a cause of the auricular fibrillation. In an inquiry into the conditions associated with fibrillation of the auricles (Lea, in this Journal, iv, 1911, p. 423), dilatation of the heart is noted as a possible cause in about 23 per cent. of the cases. In the present Case IV there was towards the end marked dilatation and hypertrophy of the left ventricle, but when first seen within a few hours of the onset the dilatation was very slight and a progressive increase was noted during his illness. It seems, therefore, justifiable to conclude that this dilatation was a consequence of the auricular fibrillation, or, at any rate, that it had nothing to do with its causation; and in this case no other sufficient cause for the onset of the fibrillation could be found. In some cases of this kind fibrosis of the myocardium of the auricles has been found after death and has been regarded as having influence in the production of the fibrillation, but the absence of such fibrosis in this case and others shows that such influence must be of the slightest. Further, at the present time no convincing theory has been advanced to explain the onset of the fibrillation. It is true that to suggest that the real cause may be found outside the heart and not in any anatomical change in the heart itself does not advance matters much, but the recognition of the possibility of this suggestion being true may direct research into a more fruitful channel. Obviously, if we acknowledge

that auricular fibrillation has in one case started in a heart that was up to that moment perfectly healthy, we must further admit that such an onset is a not uncommon clinical event, though, of course, in the vast majority of cases there is previous valvular, arterial, or myocardial disease.

It has been suggested that the sudden death, which is not a very rare termination of cases of auricular fibrillation, is due to the onset of fibrillation of the ventricles, an event incompatible with the maintenance of life. This suggestion is incapable of proof, but there is considerable probability that it is true. It is even possible that fibrillation of both auricles and ventricles may start simultaneously, thus accounting for some cases of sudden unexplained death in heart disease. If the suggestion as to the possible occurrence of auricular fibrillation in previously healthy hearts is correct, then it must be extended to the possible onset of ventricular fibrillation in healthy hearts also, and this may be the possible explanation of some cases of sudden death in people who have shown no previous sign of disease and in whose hearts nothing abnormal can be found post mortem. This is as reasonable an hypothesis as that they have died in a first attack of angina pectoris.

Conclusions are hardly justified in a subject about which so little is known, but the main points may be summed up under that heading.

Conclusions.

1. That the exact cause of auricular fibrillation is unknown.

2. That it usually comes on in a heart where there has been for a considerable period disease of the valves or myocardial change from inflammation or degeneration.

3. That it sometimes arises suddenly where there has been no previous sign or symptom of heart disease.

4. That possibly in some of these cases it occurs in hearts which were previously perfectly healthy.

5. That if this is true its essential cause must lie outside the heart and not in any anatomical or pathological change in the heart itself.

6. That sudden death in auricular fibrillation is probably due to the onset of fibrillation of the ventricles, and that some cases of sudden death both in diseased and healthy persons may be due to the simultaneous onset of fibrillation of both auricles and ventricles.

ILLUSTRATIONS OF HEART-SOUND RECORDS

By THOMAS LEWIS
(Cardiographic Department, University College Hospital Medical School [1])

With Plates 19–25

Method.

THE method employed to register the sounds produced by the heart, described in the present paper, which is very similar to that recently described by Einthoven (1) and Fahr (3), is shown schematically in Fig. 1. A large and sensitive microphone (M) communicates with the air through thick-walled rubber tubing and a stethoscope end-piece (S). The tubing has a second outlet (O), which remains permanently open. Its purpose is to avoid the combination of heart-sound record with that of slow movements of the chest wall due to the heart-beat. The microphonic circuit includes a dry cell, a make-break key (K^2), a rheostat (R=70 ohms), and the primary coil (10 ohms) of an inductorium or transformer (T). The secondary coil (coreless, 5,300 ohms) of the transformer is connected to a short circuiting key (K^1); this key, when closed, forms a shunt to the fibre of the string galvanometer (G). Sound vibrations, transmitted through the stethoscope, fall upon the microphonic plate and by pressure produce variations in the internal resistance of the microphonic circuit; the current flowing through this circuit is varied accordingly, and, varying, induces currents of higher potential in the secondary circuit; these secondary currents flow directly through the string when the shunt (K^1) is open. The string galvanometer, on account of its sensibility, readily records these currents when they flow through it. In using the string galvanometer in this manner, it is necessary that the fibre should be relatively tense. The tenser it is the more capable is it of rapid movement. I have employed the instruments modelled by the Cambridge Scientific Instrument Company, and, working with silvered glass fibres in the recording galvanometer, have found that oscillations having a frequency of 660 per second may be recorded with facility when the string is very tense. At such

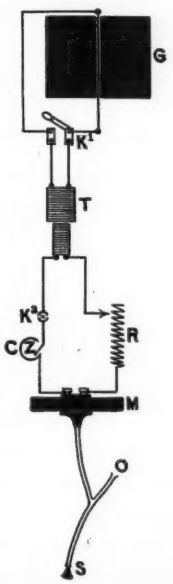


FIG. 1. A diagram of the electro-phonograph.
M = Microphone;
S = Stethoscope;
R = Rheostat;
O = Outlet;
C = Dry cell;
T = Transformer;
G = String galvanometer;
K = Keys.

[1] The expenses of this work have been defrayed by a grant from the British Medical Association.

a tension that 4 millivolts yield 1 cm. excursion, the string's deflexion time is approximately 0·004 second. The two deflexions, or a complete vibration, would occupy 0·008 second. With the string at this tension a sound having a frequency of 125 per second would be recorded at an amplitude of 1 cm. without damping. In the case of the majority of the observations here recorded the deflexion time was less ; so that vibrations having a frequency of 250 or more per second appear unchanged in the records at amplitudes of 1 centimetre and less.

The sound curves described are not standardized, so as to provide comparisons of amplitude from curve to curve, for the reason that no method of sufficient reliability is as yet available for the purpose. The excursion of the string is simply controlled so as to provide curves of suitable size for reading the events in relation to the times of their occurrence.

As the most reliable standard with which to gauge the relation of acoustic events to systole and diastole in the heart, electro-cardiograms from the second lead (right arm to left leg) have been chosen and taken simultaneously. The two installations, electro-phonograph and electro-cardiograph, are arranged side by side, the shadows of the two strings converging slightly and falling upon the

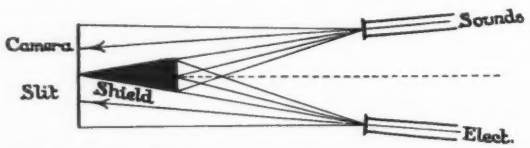


FIG. 2. A diagram illustrating the optical arrangements used in taking simultaneous electro-cardiograms and heart-sound records.

same horizontal slit (Fig. 2). To separate the light, diverging from the two eye-pieces of the galvanometers, a triangular shield is arranged with its point lying at the camera slit. Overlap of the light from two sources is thus avoided and definition of the pictures is sharp.

The plate moves at right angles to the line of the slit and is ruled (in the direction of motion) by lines drawn upon a cylindrical lens placed in the slit. These lines are seen in the figures; supposing the motion of the plate to be exactly at right angles to the slit, then any line drawn at right angles to the direction of travel will cut the two recorded curves at points representing the same instant of time. In the figures, a line at right angles to the horizontal represents a given instant with an error so small as to be negligible (the line of motion in my apparatus is not absolutely at right angles to the slit, and the heart-sound record, relative to the electro-cardiogram, is delayed by an interval of not more than 0·0005 to 0·001 second, according to the speed of the travelling plate and the distance of one record from the other).

A calculation has to be made for the transmission of the sound through the recording apparatus ; this may be measured by arranging a contact between two pieces of metal so that the contact sends a small current through one galvano-

meter while its sound is recorded by the other (Fahr). The delay of the heart-sound record in the present curves from this cause is a little less than 0·002 second. The total delay from all causes amounts to about 0·003 second. This fraction has been allowed in the calculation of intervals subsequently mentioned in this paper.

Experimental Observations.

The experiments have been conducted upon animals anaesthetized with morphia, paraldehyde, and ether. The heart-sounds have been recorded from the shaved chest wall, the stethoscope resting over the lower third of the sternum or an inch or more to the left of the sternum in the 5th or 6th intercostal space.

The heart-sounds are readily recorded in the dog; though, to obtain good records, it is necessary to eliminate breath-sounds. Artificial respiration was employed, therefore, the pump being stopped immediately before a record was taken. Simultaneous electro-cardiograms were taken from the right fore-limb and left hind-limb, and sometimes a simultaneous carotid curve from the middle of the artery in the neck by means of Hürthle's manometer. The relation of the sounds to the several electro-cardiographic deflexions is not constant. They are exemplified by the accompanying table, which also includes the approximate lengths of first and second sounds.[1] The readings are averages of a number of measurements (Figs. 3 and 4).

	Heart rate.	Commencement of Q to First Sound.	Commencement of R to First Sound.	End of T to Second Sound.	Length of First Sound.	Length of Second Sound.	Frequency of Vibrations.	
							First.	Second.
Dog DE	131	0·017	0·010 or less	−0·016	0·14	0·06	48	60
Dog DF	136	(Q) absent	0·004	−0·051	0·19	0·04	52	75
Dog DJ	121	0·024	0·018	0·023	0·13	0·09	70	89
Dog DK	130	0·029	0·027	−0·011	—	—	84	86

The first heart-sound commences 1 or 3 hundredths of a second after the upstroke of the summit R, and a little more than this after the depression Q. The second heart-sound usually begins before the end of the down-stroke of T, and this interval may extend to 0·05 second, but more commonly is much less; T may end before the second sound appears. These figures correspond very closely to those of the normal human subject. In dogs the first sound is approximately double the length of the second, and has usually double its amplitude, though the pitch of the latter is somewhat higher. In the human subject the first sound is also much louder than the second, but sometimes the reverse is true; it is also much longer than the second, but the average frequency of vibration in man is very similar for both. As regards the character of the two sounds, in both man and dogs the first sound, as is well known, is more booming to the ear, while the second has a sharper quality. The difference is

[1] The third sound has not been observed in dogs.

not constant, however, but when present it seems to result from the amplitudinal relations of the separate vibrations in the two sounds. The first sound is generally crescendo in amplitude at first and subsequently diminuendo, while the initial vibrations of the second sound are often the most intense and the sound as a whole is then a simple diminuendo (Fig. 5). The sounds begin differently but end in the same fashion.[2]

When respiration is in abeyance, the forms of the curves are wonderfully constant from cycle to cycle, the sound vibrations are usually repeated in all their detail (Figs. 3 and 4).

The influence of rise of aortic pressure upon the sounds. It is commonly taught that rises of blood-pressure produce an accentuation of the second heart-sound; certain it is that high arterial pressure is often accompanied by such accentuation, but that the last depends upon the first is clearly negatived by simple experimentation. In a number of animals I have studied the effects of a rise of blood-pressure, such as is induced mechanically by obliterating the abdominal aorta, upon the sounds, and in no instance have been able to detect any appreciable alterations; neither have I been able to hear or record any tendency to reduplication under similar circumstances. In Fig. 6 the diastolic pressure rises from 45 to 62 mm. Hg., the systolic rising from 95 to 125 mm. Hg., while the heart-sounds remain quite unchanged.

Of the factors which influence the intensity of heart-sounds none seems so important as the intactness of the chest wall. In the dog, the introduction of the smallest quantity of air has a profound damping influence, so much so that in studying heart-sounds in this animal the chest wall must be religiously respected. Repair of the chest wall does not as a rule restore the sounds. In this animal too, a number of experiments are abortive on account of the complete and unexplained loss of the second sound early in the course of the experiments.

The effects of change of rate, on the other hand, are pronounced and uniform. A rise of rate is accompanied by a diminution in the amplitude of both sounds. The duration of the sounds is much less affected (Fig. 7).

Murmurs in artificial aortic disease. The aortic valves are easily damaged by introducing suitable instruments through the carotid in the neck, and the murmurs which result in the dog are very audible over the front of the chest wall. When, as usually happens, a single cusp is pierced and torn through to its margin, the second sound is still recorded, but it is accompanied and followed by a number of fine vibrations the frequency of which is approximately 100 to 120 per second (Fig. 8). They are generally regular in incidence and uniformly diminuendo. The amplitude is never great, being far less than that of the vibrations of the second sound; it may require close examination of the curves to detect them. In a solitary experiment, in which a dorsal aortic cusp was broken, a second murmur, having a lesser frequency of vibration, appeared in

[2] The syllabic equivalent to the heart-sounds, '*lub-dup*,' is a most imperfect expression of the sounds. Records of the spoken syllables bear not the slightest resemblance to the natural sounds.

presystole (Fig. 9). In the record it clearly resembles a presystolic murmur of mitral origin and brings to mind the murmurs described in aortic disease by Flint (4).

Grouping of heart-sounds produced by irregularities. Acceleration of the heart's action has, as has been stated, a considerable influence upon the amplitude of the sounds and a lesser influence upon their duration. Now when there is an increase of rate, the pauses between the beats are reduced, and it is to this that the alteration of the heart-sounds is due. Premature contractions are preceded by relatively short pauses and the sounds which accompany them are altered, as are the sounds produced by rapid action. The sounds of a dog's heart in which occasional premature beats were excited are shown in Fig. 10. Two normal cycles are shown, and these are followed by a premature beat (of auricular origin). The premature first and second sounds are both reduced in amplitude and the duration of the second sound is curtailed. The character of the sounds is altered. The interval between first and second sounds is shortened also. The first beat after the pause is accompanied by a louder and longer first sound, but the corresponding second sound is not much affected.

If the premature beats occur very early in diastole, the first sounds are conspicuously reduced both in amplitude and duration, and may undergo a considerable change in character, while the second sound may vanish altogether. This, as is universally recognized, results from failure of the weak premature contraction to raise the aortic valves (Fig. 11). Curious groupings of the heart-sounds occur when premature beats recur frequently and in regular fashion. Two examples are shown in Figs. 11 and 12. In Fig. 11 the heart is beating in couples; a premature contraction of auricular origin follows each normal heart-cycle. The normal heart-beat is accompanied by first and second sounds, and the latter is immediately followed by and fuses with the first sound of the premature beat; the corresponding second sound is not present. The coupled heart-beats gave rise to tripled heart-sounds which were clearly audible. The reduction of the premature first sound in both amplitude and duration is conspicuous, also its character is greatly modified; it consists of three rapid and almost uniform vibrations, together occupying about $\frac{1}{30}$ second; were it longer it could not be distinguished from a murmur. Coupling of the heart-beats from the same cause and in the same animal is shown in Fig. 12; but here there is a wide gap between the individual beats of a couple. The premature beats are effective in raising the aortic valves, and the heart-sounds consequently occur in groups of four. The amplitudes of the sounds accompanying the premature beats are reduced as usual, and these systoles, as measured from the commencement of first to second sound, are relatively short.

When the auricles fibrillate and the ventricle responds irregularly, the sounds are modified accordingly. They vary in amplitude and duration and the distance between first and second sound varies in duration from beat to beat, according to the length of the preceding pauses, and when a pause is very short the succeeding second sound is absent (Fig. 13).

Clinical Observations.

The heart-sounds of the normal human subject have been described in another paper (8); so also have the acoustic phenomena in cases of mitral stenosis.

Mitral regurgitation. I have found considerable difficulty in recording the systolic apical murmur in a large percentage of cases of simple mitral regurgitation, and have been impressed by the smallness of its amplitude in most cases. We know that it often conveys the impression of distance, but until its registration was attempted I had no conception of the degree in which the first sound predominates over it. Naturally, it is often buried in the first sound, and under such circumstances may show itself in the form of small secondary vibrations upon the large vibrations of this sound. But sometimes it is almost imperceptible in the curves (Fig. 14), though clearly perceptible to the ear. In the original of Fig. 14 (S.M.), very fine oscillations can be seen, following upon the first sound; they are scarcely visible without the aid of a magnifying glass. In taking records and auscultating the chest at the same point from time to time, one is greatly impressed by the power of the human ear and centres of reception in discriminating between sound and murmur.[4] When a systolic murmur is present in conjunction with the first sound, the microphone records both; the ear detects one or other and exaggerates it according to the degree and direction in which the mind is concentrated.

A systolic murmur, occurring in mid-systole, commencing with the end of the first and ending with the commencement of the second sound, is seen in Fig. 15. It consists of fine-cut and almost uniform vibrations, having a frequency of about 112 per second. It had a very faint musical quality. Another similar example, in which the frequency is about 140, is shown in Fig. 16.

Aortic murmurs. Of aortic murmurs I have a number of records. A rough to-and-fro murmur is shown in Fig. 17. It was taken at the second cartilage, at which point neither first nor second sounds could be heard. A trace of first sound, nevertheless, is seen in the record. It is recognized by its low frequency. The vibration frequency is very variable during both systolic and diastolic phases; it averages about 80 per second. Both murmurs are diminuendo, the systolic being the louder. The two are together practically continuous, and the intensification which marks the commencement of the diastolic murmur falls very far to the left in relation to T in the electro-cardiogram.

Of loud musical diastolic aortic murmurs I have two examples: one is shown in Fig. 18. It is characterized by the *uniformity* of the vibrations, whose frequency is 138 per second. The murmur lasts about 0·24 second. In the second example in my possession the amplitude is much greater than that of the first sound; the duration is 0·14 second, and the frequency of vibration 180.

[4] This discrimination may be emphasized by the statement that, in many cases of heart affection, a continuous noise is present, even when respiration is suspended. This noise passes unperceived by the ear unless attention is specially fixed upon it.

Pulmonary stenosis and patent ductus arteriosus. The exact diagnosis of congenital heart-lesions presents many difficulties; but in one group of patients, continuous or almost continuous thrills and murmurs occur in the region of the pulmonary cartilage, and these patients, as has been emphasized by Gerhardt (5) and Gibson (7), have patency of the ductus arteriosus. The patency of the ductus may or may not be associated with stenosis of the pulmonary orifice, and, from the character of the actual murmur, the presence or absence of this second defect cannot be decided.

The continuous murmur is, as a rule, coarse and loud, and is accentuated from time to time. Its duration is also curtailed from time to time, varying both in intensity and duration with the acts of breathing and with other causes. I give several illustrations of these murmurs in Figs. 19–21. The murmur is most intense in systole and follows immediately upon the first sound. In my examples it increases in intensity during systole; it does not decrease, as does the systolic murmur of aortic disease (Fig. 17), but reaches its greatest intensity shortly before the onset of cardiac diastole (which is represented in the electric curve at or near the end of T). From this point it tails away into diastole, disappearing almost entirely before the end of diastole (Figs. 19, 20, and 21) or continuing with lesser amplitude right up to the next first sound (Fig. 20). The variations in duration and intensity from cycle to cycle are well illustrated by Figs. 20 and 21, which were taken from a single patient and are to all intents and purposes continuous curves. The vibrations of these murmurs are very irregular in position and amplitude, giving them their rasping quality. The frequency is from 100 to 130.

Forms of reduplicated sounds. In those patients from whom electrocardiograms are taken which indicate a functional defect of a single auriculoventricular bundle branch, and in whom it is supposed that the impulse travels to one ventricle only, though both eventually contract,[5] reduplication of the first sound is frequent (2). The type of reduplication is a curious one. It may be, as in Fig. 22, that the two elements are alike, each consisting of a number of slow vibrations which resemble those of normal first sounds; but the elements may be dissimilar, in which case the first element is generally of smaller amplitude than the second (Fig. 23), and of a different character. In all instances in which I have recorded the sounds (four cases) the first element has commenced before the ventricular complex, though the greater part of it coincides with the ventricular complex. The second element stands in much the same position as the normal first sound, as a rule a little later, coming either 0·05 to 0·07 second after the opening of the electric deflexions of the ventricle. The first element is properly speaking presystolic, and occurs, in part at least, coincidentally with the auricular contraction; that it is independent of the ventricular systole seems clear from its time relations. The double sound is not due, as might have been thought, to asynchronous action of the two ventricles, resulting from the abnormal path

[5] The contraction starting in the one ventricle and spreading to the other.

taken by the contraction wave, and consequent asynchronous closure of the valves. To what is it to be attributed? No very certain answer can be given to this question. If we study the reduplication shown in Fig. 22, the resemblance between the two elements is so striking that it is difficult to believe that they had a different origin. It seems probable that both resulted from closure of the auriculo-ventricular valves. It is possible that the valves close twice, once near the end of auricular systole and once at the beginning of ventricular systole, but why such conditions prevail especially in these cases of bundle branch lesion is still not apparent. These heart-sounds are often referred to by the name of 'gallop rhythm'. I have recently obtained a record from a child in which 'gallop rhythm' was audible, but this patient had normal electro-cardiograms. The time-relations of the elements were similar to those already described;[6] the presystolic element apparently is not peculiar to reduplications where bundle lesions are present. In the cases in which I have observed the abnormality of sounds, the defect has been always in the *right* bundle branch; but this has no necessary significance, for bundle defects are much more common on this side of the heart. Measurements from the four sets of curves are given in the accompanying table in seconds.

	Length of Elements.	Beginning of First Element to beginning of Ventricular Complex.	Beginning of Ventricular Complex to beginning of Second Element.	Length of P to beginning of Ventricular Complex.
Case 1.	0·20 (together)	0·03	0·07 approx.	0·15
Case 2.	0·09 0·12 (gap = 0·04)	0·07	0·06	0·16 approx.
Case 3.	0·25 (together)	0·03	0·07	0·15
Case 4.	0·17 (together)	0·04	0·05	0·16

We have seen that reduplication of the second sound may be simulated when premature beats are present. In such instances the first sound of the premature cycle follows closely upon the second of the normal cycle, and if the second premature sound is absent (Fig. 11), or is weak (as in the clinical instance, Fig. 24), the second sound of the normal cycle may appear to be reduplicated. But confusion from this source can scarcely arise except when the premature cycle falls immediately after the normal one (as in Fig. 11). An example of the reduplicated second sound of mitral stenosis was given in my earlier paper (8), and in this the elements of the double sound were close together and equal in character and amplitude.

Such reduplication has to be distinguished from the reduplication caused by the presence of what is known as the third heart-sound (6), an example of which is shown in the last figure (Fig. 25). The third sound lies in mid-diastole and, in this instance, some 0·18 second from the commencement of the second sound and during the contraction of the auricle. Generally speaking it associates

[6] In three other instances the additional sound of the 'gallop' lay in diastole, midway between second and first sounds; one of these cases was a patient who exhibited auricular fibrillation.

itself with a slow heart action and has been attributed to a secondary closure of the auriculo-ventricular valves; it possibly has this origin in some cases, but the explanation will not hold good in the present one, for as the auricles were in contraction the valves leading to the ventricles must have been patent. The auricle is known to give rise to a sound by its contraction in some cases, especially in complete heart-block,[7] and it may be that the sound of Fig. 25 is in reality of auricular origin; the time-relations certainly suggest it. But when we are dealing with so complex a movement as that of the heart-beat, the origin of abnormal sounds is often difficult to explain, and I hesitate to offer final explanations for the phenomena discussed until more material has been collected. The curves serve to illustrate the complexity of the problem of reduplication generally and to emphasize the need of studying it graphically.

[7] I have since been able to record these sounds in complete heart-block; they fall with fixed relations to those auricular systoles which occur in diastole.

REFERENCES.

1. Einthoven, *Arch. Néerland. des Sci. exactes et nat.*, La Haye, 1907, ser. 2, xii. 401.
2. Eppinger and Stoerk, *Zeitschr. f. klin. Med.*, Berlin, 1910, lxxi. 157.
3. Fahr, *Heart*, Lond., 1912–13, iv. 147.
4. Flint, *Amer. Journ. Med. Sci.*, 1862, 29.
5. Gerhardt, *Jena. Zeitschr. f. Med. u. Naturwissens.*, Leipzig, 1867, iii. 105.
6. Gibson, A. G., *Lancet*, Lond., 1907, ii. 1380.
7. Gibson, G. A., *Edin. Med. Journ.*, 1900, N. S., viii. 1; and *Med. Press and Circ.*, Lond., 1906, N. S., lxxxi. 572.
8. Lewis, *Heart*, Lond., 1912-13, iv. 241.

DESCRIPTION OF FIGURES.

PLATE 19, FIG. 3. Simultaneous electro-cardiograms, carotid curve (Hürthle), and heart-sound record, from a dog during a period of apnoea. The electro-cardiograms in this and all other figures are from lead II. The heart-sounds in this figure and in Fig. 4 were taken from the left fifth space, $1\frac{1}{2}$ inches from the middle line. The time-marker is in 1/30th seconds. The hard vertical line indicates the commencement, the vertical dotted line indicates the end of ventricular systole.

FIG. 4. Simultaneous electro-cardiogram, carotid curve (Hürthle), and heart-sound record, taken from a dog during a period of apnoea.

FIG. 5. Heart-sound record taken from the apex of a normal human subject. The first sound commences with small initial deflexions which increase in amplitude until the centre of the sound is reached, from which point they decrease. The second sound is of larger amplitude at its onset and decreases in intensity. The rate of the vibrations is very similar for first and second sounds.

PLATE 20, FIG. 6. Simultaneous electro-cardiogram, carotid curve (Hürthle), and heart-sound record, taken from a dog and showing the effects of a rise of arterial pressure resulting from obliteration of the abdominal aorta. A rise of the systolic pressure of 30 millimetres of mercury is shown. The first and second sounds retain their original amplitudes.

FIG. 7. The end of a period of tachycardia and the resumption of the normal rhythm in a dog. The tachycardia was produced by stimulating the auricle with rhythmic induction shocks by means of electrodes introduced through the jugular vein. During the period of tachycardia, the first and second sounds are reduced in amplitude and are also reduced slightly in duration.

FIG. 8. Simultaneous electro-cardiogram and heart-sound record from a dog, subsequent to the rupture of a single aortic cusp. The second sound is accompanied and succeeded by a murmur (M), which shows distinctly in the record for a period of a little more than 1/30th second. It consists of a number of quick vibrations which decrease rapidly in amplitude.

PLATE 21, FIG. 9. Simultaneous electro-cardiogram and heart-sound record, taken from the fifth left space, two inches from the middle line, from another dog, in which a dorsal aortic cusp had been destroyed. With the second heart-sound and following it is a number of rapid vibrations, giving rise to an early diastolic murmur (M), and similar to those of Fig. 8, though of longer duration. Preceding the first sound is a second murmur (PM), which has a much lower frequency and occupies the position of presystole. It varies in degree and duration from cycle to cycle. Presumably it was of the same nature as the murmur described by Flint.

FIG. 10. A heart-sound record from a dog, showing a single premature contraction of auricular origin. Accompanying the premature beat, the first and second sounds are reduced in amplitude; the interval between them is reduced; they are altered in character and slightly reduced in duration. The first sound of the post-extrasystolic contraction is increased in amplitude and duration.

FIG. 11. A bigeminal action of the heart produced in the dog by interrupted stimulation of the auricle through the jugular vein. The rate of stimulation is so arranged that a premature beat follows each normal cycle. The normal cycles are accompanied by first and second sounds. The premature cycle is accompanied by a first sound; the second is absent. The first sound accompanying the premature beat is altered in character; it is of very short duration and has a small amplitude. While the heart-beats are bigeminal, the sounds are tripled. The record resembles a reduplication of the second sound.

PLATE 22, FIG. 12. Records from the same animal, showing a bigeminal action in which the beats are more separated. Under this circumstance the premature beat gives rise to a first and second sound. The heart-sounds are consequently arranged in groups of four.

FIG. 13. Electro-cardiogram and heart-sound record from an animal in which the auricles were fibrillated by faradization through the jugular vein. The action of the heart is irregular and the amplitudes and duration of the first and second sound, and also the interval between first and second sounds, vary with the lengths of pause preceding the beats which give rise to them. From time to time, when a beat is very premature, the second sound is absent and the first sound stands alone.

FIG. 14. Simultaneous electro-cardiogram and apical heart-sound record from a patient with mitral regurgitation. The first and second sounds are shown. Following upon the first sound is a series of minute and rapid vibrations produced by the murmur (S.M.). They are just visible with the aid of a magnifying glass. The murmur was very audible.

PLATE 23, FIG. 15. Apical heart-sounds from a patient who presented a loud systolic mitral murmur. The murmur is shown at S.M. and consists of a number of rapid and almost uniform oscillations confined to mid-systole.

FIG. 16. A similar murmur (S.M.) in another patient. This murmur had a faint musical quality.

FIG. 17. A record from the aortic cartilage in a case of aortic disease, showing rough to-and-fro murmurs. There is a trace of the first sound, but it is interrupted almost immediately by a systolic murmur of diminuendo type. This is succeeded by a long diastolic murmur which at first increases in intensity and subsequently decreases.

FIG. 18. A record from a case of aortic disease, showing a musical murmur which occupies the whole of diastole. Musical murmurs are characterized by the uniformity in the position and amplitude of the vibrations of which they consist.

PLATE 24, FIG. 19. A record from a case of congenital abnormality of the heart; taken over the pulmonary cartilage. The murmur was a continuous one and seemed to be accentuated in systole and early diastole. The murmur commences near the end of the first sound; its amplitude increases until the end of systole and then decreases rapidly, to be continued throughout diastole. The first sound in this and other figures may be recognized from its position and from the relatively low vibration frequency.

FIGS. 20 and 21. Two records from a similar case. The murmur is of the same kind as that shown in the last figure. It commences immediately after the completion of the first sound, increases in intensity until the systole is almost complete, and tails away with diastole. In Fig. 20 it is continued through diastole up to the next first sound, and the amplitude is irregular. In Fig. 21 it is practically lost in mid-diastole.

PLATE 25, FIG. 22. Electro-cardiogram and heart-sound record from a patient exhibiting reduplication of the first sound. The reduplication was audible over the whole of the lower precordium, but was most conspicuous in the fourth left space two inches from the mid-line, at which point the record was taken. The first element of the reduplication lies in presystole. The electro-cardiogram is of abnormal type and indicates a lesion of the right bundle branch. (The curves from the other leads were characteristic. In lead I a conspicuous summit of long duration was followed by a broad downward deflexion; in lead III a conspicuous depression of long duration was followed by a broad upward deflexion).

FIG. 23. Similar curves in another case of the same kind. The sound record is more unsteady, but the separate elements are clearly distinguishable. The first element of the reduplication commences in presystole. (The other electro-cardiographic leads showed similar curves to those described under Fig. 22, being characteristic of a right bundle branch lesion.) The sound curve was taken from the apex beat. It shows also a finely cut early diastolic murmur; the case was one of aortic disease.

FIG. 24. Apical heart-sounds and electro-cardiogram in the human subject, showing a single premature beat of auricular origin. The premature beat is accompanied by first and second sounds; the second sound is of small amplitude. The first sound of the post-extra-systolic contraction is intensified.

FIG. 25. Electro-cardiogram and heart-sound record, taken from the apex beat of a young subject and showing first, second, and third heart-sounds. In this instance the third sound occurs during the systole of the auricle.

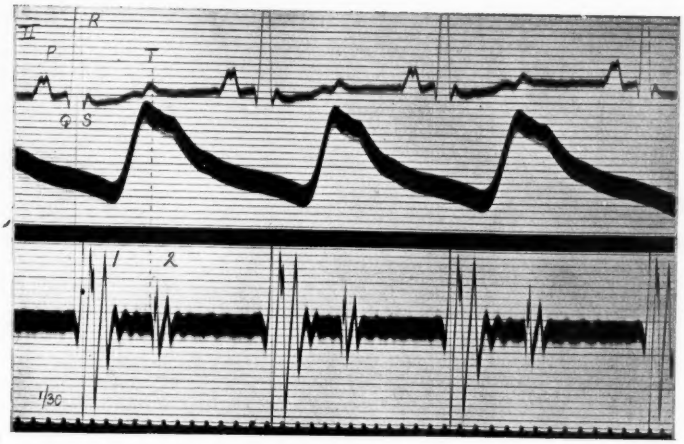


FIG. 3

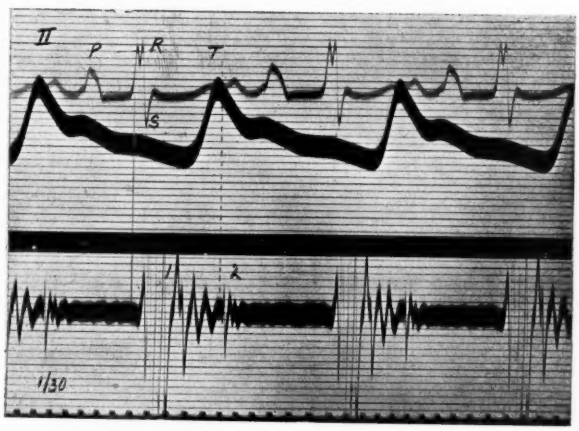


FIG. 4

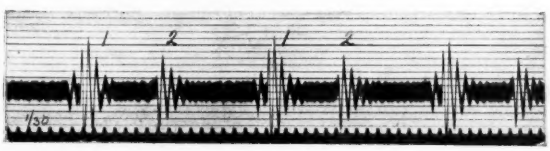


FIG. 5



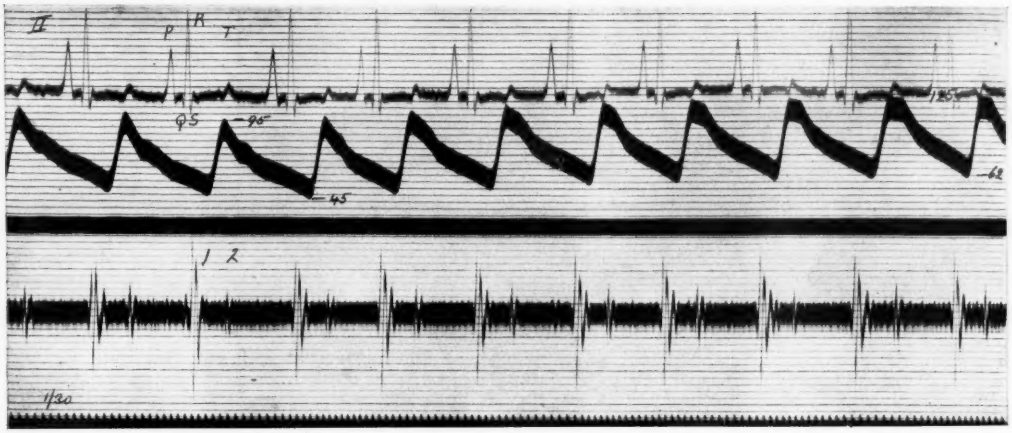


FIG. 6



FIG. 7

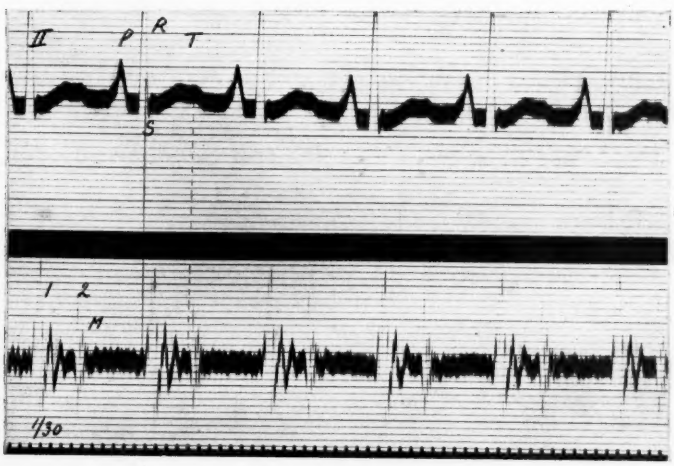


FIG. 8



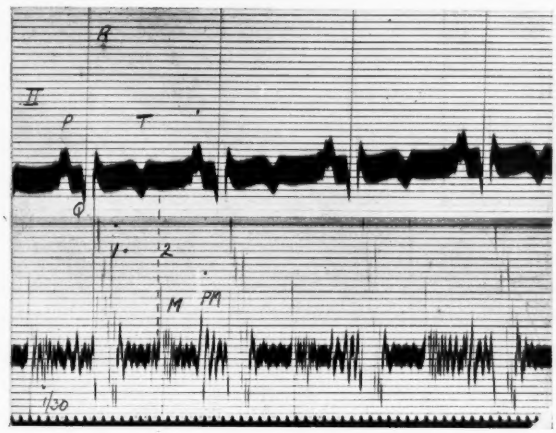


FIG. 9

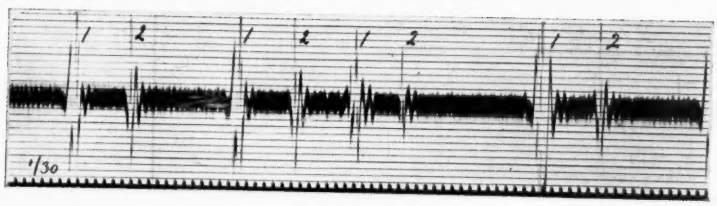


FIG. 10

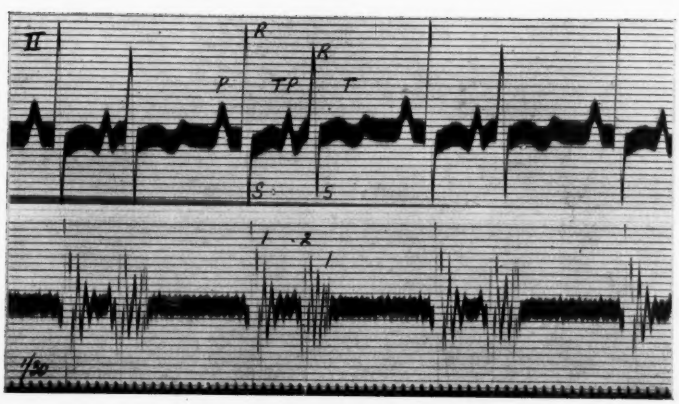


FIG. 11

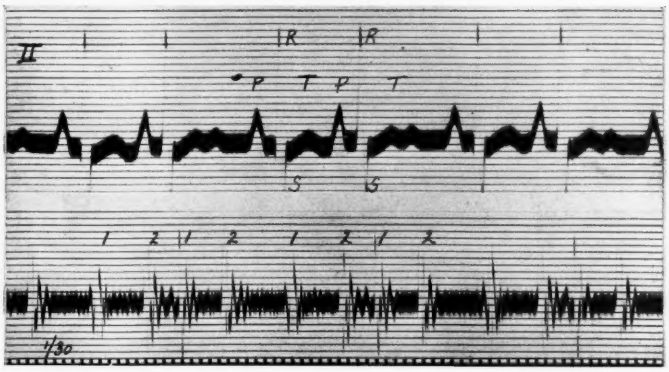


FIG. 12

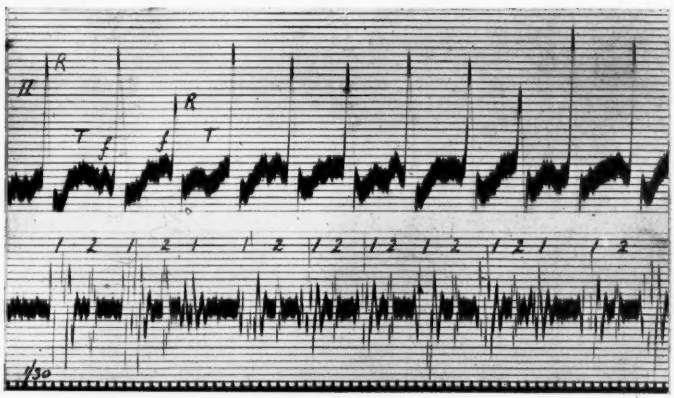


FIG. 13

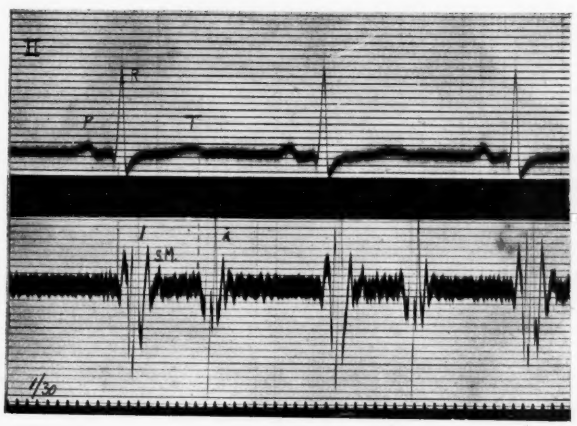


FIG. 14

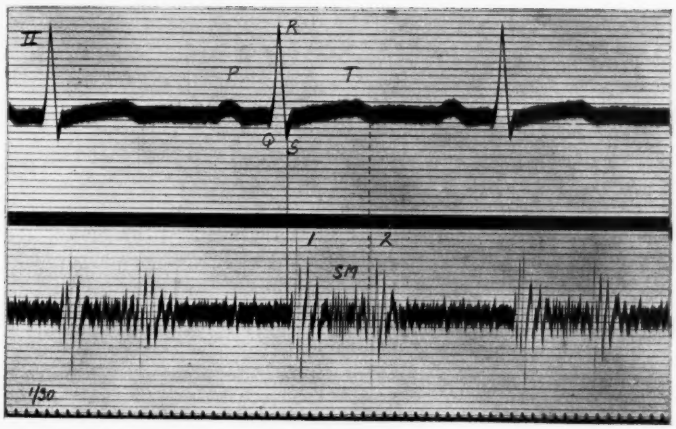


FIG. 15

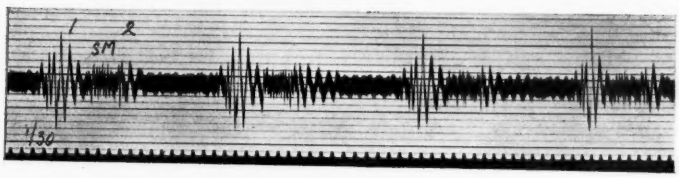


FIG. 16

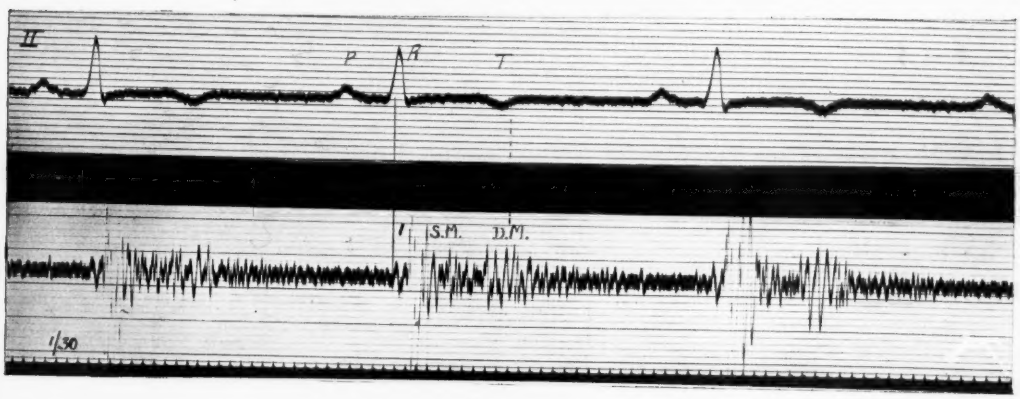


FIG. 17

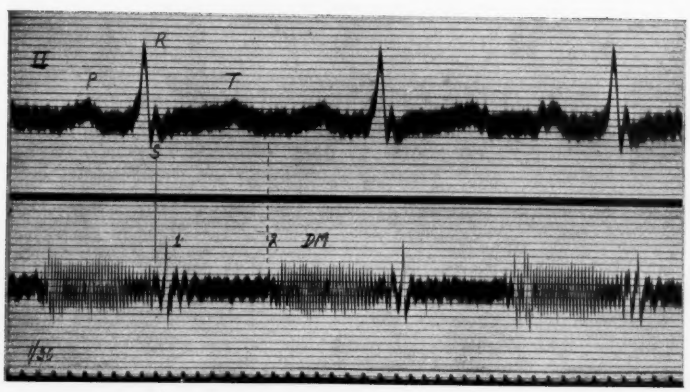


FIG. 18

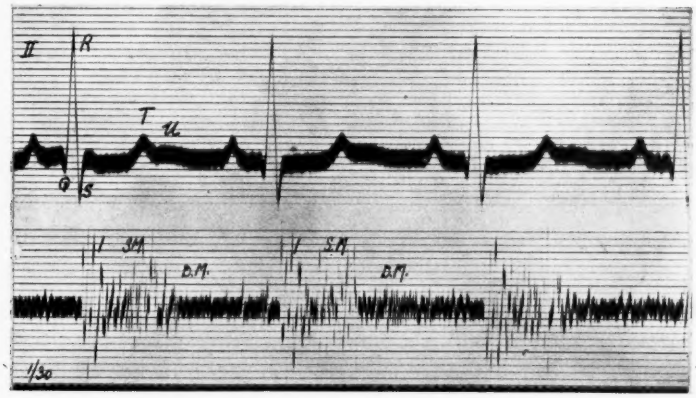


FIG. 19

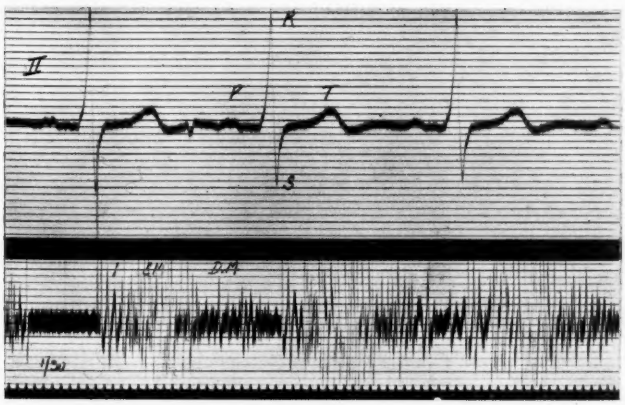


FIG. 20

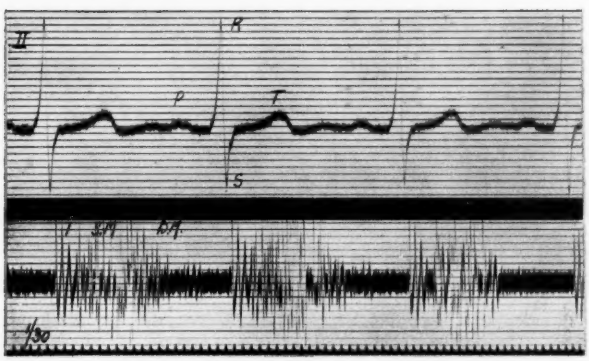


FIG. 21

Q

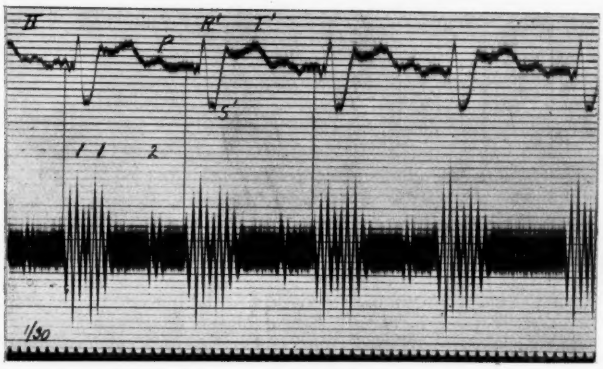


FIG. 22

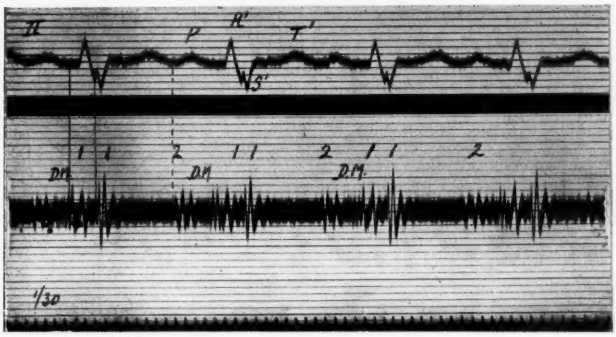


FIG. 23

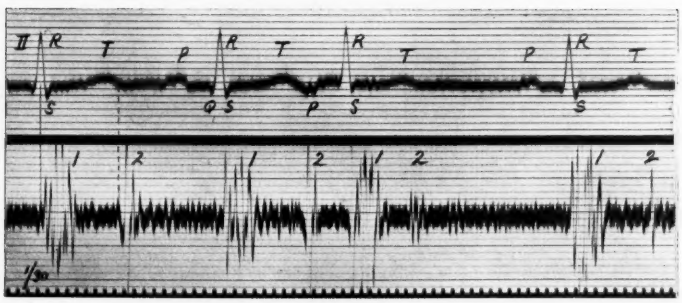


FIG. 24

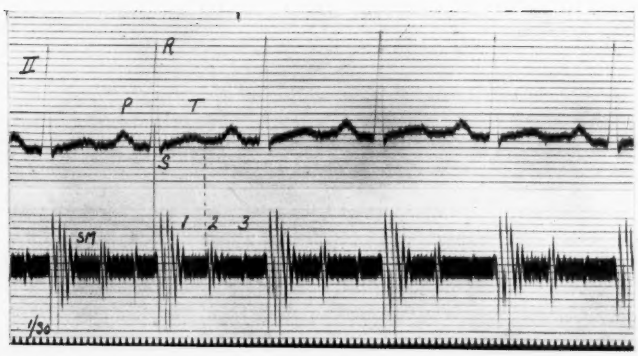


FIG. 25

THE INCIDENCE AND PROGNOSTIC VALUE OF THE PULSUS ALTERNANS IN MYOCARDIAL AND ARTERIAL DISEASE

By J. DAVENPORT WINDLE

For over four years I have been engaged in an inquiry to ascertain the value of the pulsus alternans as a sign of disease of the heart, its frequency in different conditions, and its significance for prognosis.

I have had forty-five patients under observation, showing the pulsus alternans in the following conditions, stated here in order of frequency. (1) Arterial and myocardial disease. (2) Chronic heart disease due to rheumatism. (3) Pneumonia. (4) Paroxysmal tachycardia. (5) Acute rheumatic carditis.

This paper is to summarize some preliminary observations respecting the cases comprised in the first group.

I.

Frequency of the pulsus alternans in myocardial and arterial disease. Some authors state the pulsus alternans is a common symptom in the form of heart disease in question, and that it has no particular significance, but from the succeeding account it is evident those advancing these opinions are unacquainted with the characters of pulsus alternans properly so called. They describe and illustrate under this name irregularities in force of the pulse of entirely different nature and significance; as, for example, extra-systolic bigeminy of the pulse and complete irregularity of the pulse.

In the more recent literature on the subject many writers go to the other extreme of opinion, in that the pulsus alternans is said to be a rare phenomenon and invariably a fatal sign. In my own experience, while the pulsus alternans is not very common, yet it is far from rare. My records of 202 aged people examined in private and hospital practice[1] show that it occupies the third place in order of frequency of irregularities of the pulse, being preceded by extra-systolic irregularity and complete irregularity of the pulse and followed by irregularity due to impaired *a.–v.* conduction, complete heart-block, and sinus irregularity, in this order of frequency.

[1] Hospital patients were those examined in the out-patient and in-patient departments of Mount Vernon Hospital during routine work as clinical assistant to Dr. James Mackenzie from November, 1909, to the present.

TABLE I.

Pulse irregularities observed in 202 cases of arteriosclerosis.

Nature of Irregularity.	Number of Cases observed.	Percentage.
Extra-systoles	109	54·5
Complete irregularity	61	30·5
Pulsus alternans	23	11·5
Impaired *a.-v.* conduction	3	1·5
Partial heart-block	1	0·5
Complete heart-block	4	2·0
Sinus irregularity	1	0·5

I believe the position occupied by pulsus alternans in this table is approximately its true one, although the percentage is far in excess of what it is generally thought to be. Dr. Mackenzie tells me that the table is in close agreement with his figures. He finds the pulsus alternans is present in myocardial disease much more commonly than is usually supposed, and he agrees with me that its ascribed infrequency is due to the fact that it is often overlooked and not sought for in the same patient under different circumstances.

II.

The prognostic significance of the pulsus alternans in arteriosclerosis. My experience is that the presence of the pulsus alternans in a case of myocardial and arterial disease always adds to the gravity of the prognosis. It signifies disease of the heart progressing inevitably to a fatal end; and this is its meaning when present, as it not seldom is for a time, in patients whose clinical condition does not suggest serious unsoundness of the heart.

In the following summarized histories of thirty-three patients with myocardial and arterial disease under my own observation, the diagnosis of the pulsus alternans was established in each case by polygraph tracings; and records were taken systematically during the time the patients were under notice.

Abstract of clinical notes in thirty-three cases of Pulsus Alternans.

Case 1. B., female, aged 65 years. Previous history good. Complained only of breathlessness on exertion; healthy looking; no symptoms at rest. Heart not enlarged; arteries diseased; pulse regular at rest and after exertion. Systolic blood-pressure 185. No albumin. Subsequently continuous pulsus alternans developed. Cheyne-Stokes breathing occurred as an incidental symptom. Severe dropsy set in; improvement for a time. Attacks of cardiac asthma and precordial pain ensued; dropsy recurred. Fatal 2 years after pulsus alternans first noticed.

Case 2. K., male, aged 72 years. First seen for an attack of bronchitis; previously always healthy. Some weeks after he recovered brief pulsus alternans after extra-systoles was first noticed. Heart a little enlarged; arteries diseased. Blood-pressure 186. He continued at light work on and off for some months subsequently; became very breathless. Heart more enlarged, continuous pulsus

alternans present. Dropsy set in; under digitalis improved for a time. Attacks of cardiac asthma occurred; Cheyne-Stokes breathing when asleep; dropsy recurred. Died thirteen months after pulsus alternans was first observed.

Case 3. L., male, aged 63 years. Complained of indigestion; heart slightly enlarged; arteries very tortuous. Blood-pressure 200. Pulse quite regular; later attacks of angina pectoris; heart more enlarged and murmurs heard, pulsus alternans present after exertion. Albumin in urine. Attacks of cardiac asthma became frequent; subsequently severe dropsy set in. He recovered under digitalis treatment sufficiently to resume work for a time. Attacks of angina pectoris recurred, and he again became dropsical; continuous pulsus alternans present. Cheyne-Stokes breathing continued for five days. Fatal from acute oedema of lungs eighteen months after pulsus alternans was first observed.

Case 4. S., male, aged 72 years. Breathless on going uphill. Very healthy looking man; never had a day's illness. Heart not enlarged; arteries tortuous. Blood-pressure 180; pulse quite regular. No albumin. Improved with rest. Symptoms recurred; extra-systoles in pulse followed by alternation present for first time. Kept in bed for three weeks, greatly improved. For eight months he was able to go about quite well and take walks of half a mile without much distress. During this time was seen off and on and pulsus alternans found present on exertion. Attacks of cardiac asthma ensued; heart considerably enlarged; continuous pulsus alternans present; dropsy of feet and legs. Had marked Cheyne-Stokes breathing for three days before death, which occurred ten months after pulsus alternans was first observed.

Case 5. K., female, aged 63 years. First seen after an attack of pain in chest and down both arms after hurrying to church. A healthy looking, active woman; no previous illness, no symptoms at rest. Had been short of breath on exertion for some time. Heart somewhat enlarged; pulse regular in force and rhythm; arteries diseased. Blood-pressure 230. No albumin. No further attacks of pain; cardiac asthma at night set in some weeks later; during these attacks continuous pulsus alternans was present at first, passing off with the attack; later on was permanent. She had constant periodic breathing for some months when at rest; heart further enlarged, severe dropsy set in. Fatal twenty-four months after pulsus alternans was first noticed.

Case 6. B., male, aged 79 years. Pain in chest after hurrying to catch a train. Very healthy looking man, no previous illness of moment; breathless on undue exertion for some time. Heart not enlarged; an occasional extra-systole in pulse, no alternation; arteries diseased. Blood-pressure 170. No albumin. Led a quiet life, had no further attack of pain; breathlessness became worse, extra-systoles more frequent; after exertion marked pulsus alternans present. Later on dropsy set in; pulse completely irregular in rhythm for a few weeks before death. Marked Cheyne-Stokes breathing was present the day he died. Fatal ten months after pulsus alternans was first noticed.

Case 7. W., male, aged 65 years. Complains of frequency of micturition; has been seen for 'winter cough' the last two or three years; never any illness of moment. Healthy looking. On routine examination pulsus alternans after extra-systole was noticed; no irregularity was observed before. Heart not enlarged; arteries diseased and tortuous. Blood-pressure 280. No symptoms referable to the heart; not the least breathless on severe exertion. Continues his work as a labourer. No change noticed in cardiac condition or symptoms for four months; he then complained of occasional pains at the heart and some shortness of breath at his work. At the last examination he had pronounced

pulsus alternans after exertion—that is to say, seven months after first coming under notice; he was more breathless, but able to keep at work.

Case 8. Q., female, aged 73 years. Complained of cough and breathlessness. Seen occasionally for these symptoms for two years. Healthy looking, able to go about and do light housework without distress. Heart not enlarged; arteries very tortuous; pulse regular at rest. After exertion extra-systoles followed by alternation occur. This was first noticed in August, 1912. No material change in condition has occurred up to the present—that is to say, five months after pulsus alternans first occurred.

Case 9. P., female, aged 63 years. First seen for double glaucoma. Previous health good. Three months after operation complained of breathlessness on exertion. Heart slightly enlarged; arteries diseased; pulse regular at rest. On exertion extra-systoles followed by pulsus alternans; pulse previously always regular. Continued fairly well for nine months; was able to go about on the level without much distress, and seemed well when at rest. Progressive heart-failure set in. At the present time, nine months after the pulsus alternans was first noticed, the heart is greatly enlarged, there is considerable dropsy present, and much cyanosis of face and extremities. Cheyne-Stokes breathing has been present on and off. (Patient died shortly after the note was written.)

Case 10. B., female, aged 62 years. Had previously always had good health. Pain in chest and short of breath on exertion for the last six months. Heart enlarged; mitral systolic murmur; arteries very tortuous; pulse at rest 50 per minute; on slight exertion there are occasional extra-systoles followed by pulsus alternans. Blood-pressure 145. No albumin. Under observation for a few weeks; improved very much. Not seen again for ten months; heart greatly enlarged, liver enlarged and pulsating, and dropsy present. Rate of heart 180 per minute; pulsus alternans marked. Improved for a time under digitalis, but relapsed and died twenty-one months after first coming under observation.

Case 11. Male, aged 85 years. Always a very healthy man; does very light work on the public roads. Seen after an attack of pain in the chest and down both arms, which came on at work; constantly breathless; heart enlarged; arteries diseased; blood-pressure 225; continuous pulsus alternans present; severe dropsy set in; pulse became completely irregular in rhythm. He died three months after first coming under observation.

Case 12. K., female, aged 58 years. Robust, healthy looking woman; complained of severe pain in the chest and suffocating feeling on exertion present on and off for a year; these symptoms occurred frequently; had never had to keep her bed for illness. Heart enlarged; systolic murmur over aortic area; arteries diseased; blood-pressure 157; pulse at rest regular; after slight exertion frequent extra-systoles and pulsus alternans. After complete rest for a fortnight greatly improved; she died suddenly a month after first coming under my care. On the morning of the day she died a tracing of the pulse showed it to be quite regular at rest and the irregularity after exertion not so great as at first; the same night whilst undressing she had an attack of severe pain in the chest and vomited twice; when I arrived she was obviously *in extremis*, the pulse was completely irregular in rhythm at about 130 per minute, and continued so until she died two hours later.

Case 13. M., female, aged 68 years. Healthy looking active woman; short of breath on undue exertion for some months, but could take long walks on the level; complained of pain at the chest and a suffocating feeling on going upstairs.

Heart much enlarged, loud rough mitral systolic murmur; arteries diseased; pulse regular at rest, irregular and alternating after going up and downstairs. Blood-pressure 195. No albumin. Breathlessness became extreme; severe dropsy set in. She died six months after first coming under my notice.

Case 14. M., female, aged 69 years. Healthy looking woman, never had any serious illness, but in recent years had had attacks of rheumatic gout in fingers and knees. During one of these attacks the pulse was found irregular and the tracing showed a tendency to alternation after the premature beats. She improved under treatment. Six months later she became very short of breath on exertion; the heart was slightly enlarged; pronounced pulsus alternans after extra-systole present. Blood-pressure 192. Present condition—seventeen months after pulsus alternans was first observed—she looked well, and said she felt well when at rest, but was extremely breathless on exertion and was only able to go about the house very quietly.

Case 15. E., male, aged 65 years. Hospital patient brought by Dr. Hutchison. A spare, healthy looking man. Occasional attacks of pain in chest and down *left* arm as far as elbow. Heart not enlarged; arteries diseased; pulse regular at rest, irregular and alternating after exertion. Blood-pressure 148. Seen again a year later; in the interval had had two attacks of angina pectoris with pain down *right* arm. Heart slightly enlarged; somewhat breathless on exertion; pulse still irregular and alternating. Blood-pressure 175. Dr. Hutchison informs me his condition at present is much the same. Under observation eighteen months.

Case 16. C., female, aged 54 years. Hospital patient; looks much older, but healthy. More or less short of breath for five years; lately breathlessness extreme on the least exertion; attacks of cardiac asthma; swelling of the feet. Heart slightly enlarged, arteries diseased; pulse, numerous extra-systoles followed occasionally by *slight* alternation. Blood-pressure 180. She improved very much under treatment and was discharged two months later. I examined this patient a year later; the heart was more enlarged; she was extremely breathless and scarcely able to walk about. Alternation in the pulse was much more continuous and pronounced. She wrote recently, 'I am much about the same, and some days I get very bad turns.' Under observation two years and seven months.

Case 17. I., male, aged 33 years. Hospital patient. Tall, spare, pallid man, who came for examination because of refusal for life assurance. Said he felt well and able to do his work as a clerk without discomfort. Heart considerably enlarged, double aortic murmur present; arteries thickened; pulse regular at rest; breathless after exertion and frequent extra-systoles followed by brief but pronounced alternation. Severe dropsy subsequently set in. Fatal nine months later.

Case 18. M., female, aged 68 years. Short and stout, with florid complexion. Short of breath and headaches. Heart enlarged: arteries thickened; pulse regular. Blood-pressure 200. Albumin in urine. Under observation for some months; became comatose; had marked Cheyne-Stokes breathing for sixteen days. During this time pulsus alternans was present; she recovered sufficiently to do her house-work. Subsequently became very breathless, pulse irregular, due to extra-systoles and alternation. She passed out of my care; died six months later from heart disease and dropsy.

Case 19. M. E., male, aged 58 years, looks 70. Complaint of shortness of breath and pain in chest; able to go about the house and take short walks.

Heart greatly enlarged; aneurysm of aorta (?); arteries diseased; pulse quite regular at rest, extra-systoles with alternation after slight exertion. Died suddenly ten weeks after first coming under observation.

Case 20. C., male, aged 52 years. Hospital patient. No previous history of importance. Attacks of pain in chest and neck and down left arm for two years. Slightly short of breath at rest. Heart enlarged, no murmurs; arteries thickened, arcus senilis well marked; pulse regular at rest, but markedly alternating after exertion. Blood-pressure 140. Case lost sight of.

Case 21. G., male, aged 42 years. Dr. Philips's patient. Specific history. Confined to bed for some weeks; short of breath; dropsy of legs and feet. Heart greatly enlarged; diastolic and systolic aortic murmur; arteries thickened. Pulse quite regular in rhythm; occasional short periods showing alternation. Fatal some weeks later.

Case 22. H., female, aged 62 years. Short of breath for two months, now got suffocative attacks on going upstairs; had to stop and fight for her breath; after a bad attack she broke out into a cold sweat and felt very exhausted. At rest looked well. Heart not enlarged; arteries diseased; pulse regular. Dyspnoea very severe after going up and down a few stairs and pulse became irregular and markedly alternating. Blood-pressure 215. Kept in bed three weeks; much improved; at the end of six weeks was able to go upstairs without much distress. Removed from my neighbourhood shortly after this time. I am informed she died suddenly nine months after first coming under my care.

Case 23. N., male, aged 78 years. First seen during an attack of asthma. The tracing taken showed the pulsus alternans. Next morning he was well again and the pulsus alternans had disappeared. A spare, healthy looking man, health good up to a year ago; since then occasional attacks of laboured breathing at night; somewhat short of breath at rest, but able to take fairly long walks on the level. Arteries very tortuous. Heart slightly enlarged; no irregularity in pulse at rest or on exertion. Later extra-systoles were present and pulsus alternans followed; he became more breathless, but the asthmatic attacks less frequent. Case lost sight of, but I learn his condition is much the same. Under observation eighteen months.

Case 24. M., male, aged 69 years. First seen for bronchitis, temperature raised, moist sounds all over chest. Retired from business two years previously because of angina pectoris. Heart much enlarged, loud systolic mitral murmur; arteries diseased; pulse regular. Three months later became short of breath and feet swelled; pulse was irregular at rest, due to extra-systoles followed by alternation. Blood-pressure 145. Dropsy increased and general condition became very bad. Under large doses of digitalis he improved remarkably, and at the end of three months was able to go downstairs. At the time of writing he was extremely breathless with the least exertion and unable to leave his room. There was some swelling of the feet, the pulse was irregular and alternating. During the two years he had been under observation pulsus alternans had been present one year and nine months.

Case 25. Male, aged 64 years. First seen with Cheyne-Stokes breathing following an attack of angina pectoris; pronounced pulsus alternans was present, which continued until he died. Cheyne-Stokes symptoms lasted for five days; they then ceased and there was no recurrence until his death, which occurred on the twelfth day of the illness. A tall, spare man, looked much older than his stated age. Had attacks of angina pectoris for a year. Heart much enlarged, soft mitral systolic murmur; arteries thickened and tortuous. Blood-pressure 160; urine loaded with albumin.

Case 26. E., female, aged 78 years. Under my observation at times for about two years; general health good on the whole; had but few symptoms; breathless on exertion. Heart enlarged; arteries thickened and tortuous; arterial tension high; no blood-pressure readings taken. A week after convalescence from an influenzal cold laboured breathing came on suddenly during the night; the pulse-tracing showed extra-systoles followed by alternation. Later breathing of Cheyne-Stokes character occurred, alternation in pulse was more pronounced and continuous. Next day marked Cheyne-Stokes breathing set in; she died the day following.

Case 27. Male, aged 68 years. Hospital case. Labourer; breathless at work for three months; previous health good; no symptoms at rest. Heart slightly enlarged, no murmurs; arteries diseased; pulse regular. Blood-pressure 185. No albumin. Breathing laboured after walking from one room to another. Occasional extra-systoles followed by brief alternation. No material change while under observation (five months).

Case 28. B., female, aged 65 years. Seen in consultation with Dr. Thompson. Hemiplegia five days previously; semi-conscious. Cheyne-Stokes breathing, continuous pulsus alternans; no irregularity in rhythm. Heart enlarged; arteries diseased. No albumin. Died three days later.

Case 29. E., female, aged 60 years. Short, stout, and unhealthy looking. Under observation on and off three years. Heart enlarged; arteries diseased; pulse always regular. Albumin in urine. Became unconscious with marked Cheyne-Stokes breathing; pulsus alternans present for first time. Died three days after onset of these symptoms.

Case 30. R., male, aged 62 years. A tall, well-built, healthy looking man. Complains of cough and shortness of breath; previous health very good. Breathing easy at rest, no physical signs in lungs; heart slightly enlarged; pulse, occasional extra-systoles followed by brief alternation. With slight exertion breathing distressed, pulse more irregular and alternating. Improved considerably for a time. Hemiplegia with pronounced Cheyne-Stokes breathing (for twenty-four hours) occurred. A fortnight later was much better; then cough with copious expectoration ensued. Pulse was very irregular and alternating; he became progressively worse and died at the end of two weeks—that is to say, four months after first coming under observation.

Case 31. B., female, aged 72 years. An active, healthy looking woman, under my care for gout and eczema for some years. No cardiac symptoms; heart not enlarged; arteries tortuous and tension high. Pulse at rest regular, but after exertion or with excitement extra-systoles occurred, but there was no alternation. Symptoms indicative of cancer of the large bowel occurred. The surgeon called in advised operation; she refused to have this done and was very much worried about it. She became very breathless and the pulse was now very irregular and alternated persistently; she had to take to bed and gradually became weaker, and died a month later. Cheyne-Stokes breathing was present on and off, especially during sleep, for a week before she died.

Case 32. C., male, aged 52 years. A tall, healthy looking man, complained of giddiness. Never had any illness; continued his work as a labourer; was slightly short of breath, but not enough to interfere with his work. Pulse regular at rest; decided and continuous pulsus alternans on exertion. Heart not enlarged; no murmur; arteries thickened. Blood-pressure 195. No albumin. Under observation one month.

Case 33. B., female, aged 75 years. Under my care for some months for suffocative attacks and breathlessness on exertion; otherwise health good.

TABLE II.

Cases still under observation.

Case No.	Sex.	Age.	Heart enlarged.	Arteries.	Blood-pressure.	Albumin.	Dropsy.	Symptoms.	Pulsus alternans, present.	Time under Observation.	Present Condition.
*24	M.	69	yes	diseased	145	yes	yes	angina pectoris	1 year 9 months	2 years 3 months	severe heart failure
*7	M.	65	no	tortuous	280	no	no	none	7 months	3 years	somewhat breathless
*8	F.	73	no	tortuous	not taken	no	no	breathless on exertion	6 months	6 months	no change
16	F.	54	yes	diseased	180	no	yes	breathlessness	1 year 7 months	2 years 7 months	severe heart failure
23	M.	78	slightly	tortuous	not taken	no	no	asthma	18 months	18 months	very breathless on exertion
32	M.	52	no	tortuous	195	no	no	giddiness	1 month	1 month	no change
*14	F.	69	slightly	thickened	192	no	no	gout	17 months	23 months	very breathless
15	M.	65	no	diseased	148	no	no	angina pectoris	18 months	18 months	more breathless, otherwise no material change
20	M.	52	yes	diseased	140	no	no	angina pectoris	seen once only	--	case lost sight of
27	M.	68	yes	diseased	185	no	no	breathlessness	5 months	5 months	breathlessness worse, otherwise no material change

TABLE III.

Fatal cases showing pulsus alternans at first examination.

Case No.	Sex.	Age.	Heart enlarged.	Arteries.	Blood-pressure.	Albumin.	Dropsy ensued.	Result.	Pulsus alternans present.	Time under Observation.
10	F.	62	yes	very tortuous	145	none	yes	fatal	21 months	21 months
16	M.	85	yes	diseased	225	yes	yes	,,	3 months	3 months
12	F.	58	yes	,,	157	none	no	,,	1 month	1 month
13	F.	68	yes	,,	195	none	yes	,,	6 months	6 months
17	M.	33	yes	,,	not taken	none	yes	,,	9 months	9 months
19	M.	58	yes	,,	not taken	none	no	,,	10 weeks	10 weeks
22	F.	62	no	,,	215	none	no	,,	9 months	9 months
25	M.	64	yes	,,	160	yes	no	,,	12 days	12 days
26	F.	78	yes	tortuous and thickened	not taken	none	no	,,	3 days	2 years
28	F.	65	yes	diseased	not taken	none	no	,,	3 days	—
29	F.	60	yes	,,	not taken	yes	no	,,	3 days	3 years
30	M.	62	yes	,,	not taken	none	no	,,	4 months	4 months
33	F.	75	yes	hard and tortuous	195	none	no	,,	4 days	some months

TABLE IV.

Fatal cases in which the inception of the pulsus alternans was observed.

Case No.	Sex.	Age.	Heart enlarged.	Arteries.	Blood-pressure.	Albumin.	Dropsy ensued.	Result.	Pulsus alternans present.	Time under Observation.
1	F.	65	no	diseased	185	none	yes	fatal	2 years	2 years and 2 months
2	M.	72	slightly	,,	186	none	yes	,,	13 months	17 months
3	M.	63	yes	,,	200	yes	yes	,,	18 months	20 months
4	M.	72	no	tortuous	180	none	yes	,,	10 months	12 months
5	F.	63	yes	diseased	230	none	yes	,,	2 years	2 years 8 months
6	M.	79	no	,,	170	none	yes	,,	10 months	18 months
9	F.	63	yes	,,	not taken	none	yes	,,	9 months	13 months
18	F.	68	yes	thickened	200	yes	yes	,,	9 months	about 18 months
31	F.	72	no	tortuous	not taken	none	no	,,	1 month	2 months

Heart somewhat enlarged; arteries hard and tortuous; blood-pressure 195; pulse always regular in force and rhythm. Urgent dyspnoea ensued suddenly; the pulse-tracing now showed alternation in force, very pronounced after extra-systoles, which occurred frequently; breathlessness continued for four days, when the lungs became engorged and the patient died. Pulsus alternans was present throughout.

Patients still under observation are embodied in Table II. The onset of the pulsus alternans was observed in those cases marked with an asterisk; in the others it was present when the patients were first seen.

In Table III are included fatal cases in which the pulsus alternans was present in each patient when first coming under notice. For how long it had been so in any one cannot be said. One patient lived nearly two years, the rest died in under a year. Table IV comprises the nine cases ending fatally which were under my care before the pulsus alternans occurred. This clinical course was observed from the beginning to the end, and the time of the inception of the pulsus alternans was known within narrow limits. Five of these patients died within a year; two lived eighteen months, and two twenty-four months after the pulsus alternans first showed itself.

These results support the teaching of Dr. Mackenzie. In his experience the inception of the pulsus alternans in aged people has invariably been followed by fatal heart failure within two or three years.

There was no evidence of disease on clinical examination of any one of the patients included in Table IV in the earlier stages of the illness, except the presence of the pulsus alternans, to warrant a grave view being taken of the prognosis.

When once the pulsus alternans appears in a patient the subject of arterial disease it will never again be absent for long. The reason for its permanence in these cases is that the exhaustion of the heart which it expresses is due to degeneration of the heart muscle.

In the early stages alternation becomes latent for a time through bodily rest, or the action of drugs which slow the heart, but eventually persists with rest and in spite of any measures of treatment yet tried.

PSEUDOCHYLOUS BODY FLUIDS

By JOHN MARRACK

From the Hale Clinical Laboratory, London Hospital

MILKY-LOOKING ascitic fluids occur in several conditions, which are not apparently associated with obstruction or rupture of lymphatics; cirrhosis of the liver, for example, is one of the commonest.[1] Similar fluids have also been found in the pleural and pericardial cavities. These fluids differ in composition from chyle, and have been called pseudochylous in contradistinction to collections of fluid formed by escape of lymph. Unlike the chylous, these pseudochylous fluids are not cleared by shaking with ether, but the milkiness is generally ascribed to the presence of lipoid either in excess or in some abnormal state. A large number of investigations have been performed bearing on this question.[2]

I have examined two ascitic fluids:

Case 1. Elizabeth Fuller, age 48, was admitted to the London Hospital with a history of abdominal swelling dating from her last confinement six years before, and abdominal pain and gastric disturbance of about a year's duration. On admission she had marked ascites and oedema of the whole body up to the level of the clavicles; the oedema was most marked in the legs and the face unaffected. Albumin was present in the urine in very varying quantities, but blood and casts were never found. Three weeks after admission laparotomy was performed; the peritoneum was red, and on it were seen transparent nodules the size of peas. The patient was discharged without a definite diagnosis being formed.

558 oz. of fluid were removed by tapping. This fluid was milky, soon after removal alkaline to litmus but not to phenolphthalein; about one week later also alkaline to phenolphthalein. The milkiness was not affected by centrifugalizing filtration, nor by shaking with china clay or charcoal with subsequent centrifugalizing; unaffected by adding hydrochloric acid, caustic potash, or acetic acid in varying dilutions, and not cleared by diluting with distilled water nor with 0·9 per cent. sodium chloride. On addition of an equal quantity of absolute alcohol a bulky precipitate was formed and the filtrate was quite clear. On

[1] A list of recorded cases and the disease present is given by Wallis and Scholberg (4).

[2] Bernert (1) publishes a summary of a large number of more or less complete analyses.

[Q. J. M., July, 1913.]

boiling, with the addition of a few drops of acetic acid while boiling, a precipitate formed and the filtrate was almost quite clear; on saturating the filtrate with ammonium sulphate a further precipitate was formed and the filtrate was quite clear. On half saturation with ammonium sulphate a slight precipitate formed and the milkiness of the fluid was much reduced; with two-thirds saturation a larger precipitate was formed and the fluid was cleared more; while with full saturation the fluid was completely cleared. On pouring water on the filter paper containing the precipitate formed by saturating with ammonium sulphate, a milky fluid came through the paper; this fluid was not cleared by centrifugalizing. After standing with ether for several days the fluid was not cleared and no lipoid was contained in the ether. From the precipitate formed by boiling with acetic acid about 0·09 per cent. of fatty substance was extracted by shaking with ether.

Case II. Leonard Timms, age 19, was admitted to the London Hospital on May 22, 1912, and operated on at once; a sloughing appendix was removed and the wound drained.

On June 18 a liver abscess was opened by resection of the eighth rib; bile was discharged through the wound for a week. Later he developed ascites and was tapped on July 22; 28 oz. of fluid were removed. The fluid was milky; cultures from it were sterile; it contained lymphocytes and a few endothelial cells.

The general characters of this fluid were the same as those of the last, except that the fluid was completely cleared by boiling with acetic acid, and that it was cleared by half saturation with ammonium sulphate though not by one-third saturation; it was also cleared by dialysis. The precipitates formed by half saturation and by dialysis dissolved partly on shaking with 0·9 per cent. sodium chloride solution to form milky fluids which were not cleared by centrifugalization.

The quantitative analysis of the fluid was as follows:

Total solids	2·27 %	
Ash	0·69 %	
Coagulable protein	0·95 %	Depression of freezing-point, 0·70°
Globulin by half saturation	0·49 %	
Chloride as sodium chloride	0·44 %	Specific gravity, 1014
P_2O_5	0·0126 %	
Lipoid	0·22 %	
Phosphatide as lecithin, about	0·005 %	
P_2O_5 in lipoid	0·0006 %	

[The lipoid was extracted continuously with alcohol thus: the fluid was dried by mixing with exsiccated sodium sulphate, and the powder thus formed hung in a Soxhlet thimble under a condenser; in a flask below alcohol was boiled, the vapour of which was condensed in the condenser and dropped down on to the powder. The alcoholic extract was evaporated and the residue extracted with ether.]

On shaking with ether for a short time no lipoid was extracted; 400 c.c. of the fluid were stood, with occasional shaking, under ether for fourteen days. Three layers of fluid formed; the upper consisting of 600 c.c. of ether, the middle of 120 c.c. very milky-looking gel, the lower 390 c.c. greenish fluid, only very slightly milky. The ether contained in the middle layer was evaporated, leaving 30 c.c. of a very milky fluid, which was not cleared by centrifugalizing although a scum formed.

This milky fluid contained:

Total solids	6·60 %
Total P_2O_5	0·0745 %
Lipoid	1·92 %
P_2O_5 in lipoid	0·008 %
Phosphatide as lecithin, about	0·07 %

The ether in the upper layer contained 0·369 gm. of lipoid and no phosphatide. The lower layer contained:

Total solids	1·6 %	
Total P_2O_5	0·0062 %	
Coagulable protein	0·53 %	
Globulin	0·325 %	
Lipoid	0·018 %	containing no appreciable amount of P_2O_5.

Thus the ether on long standing extracted some of the lipoid but no phosphatide; the removal of the milkiness from the main bulk of the fluid was associated with the removal of most of the lipoid and of about equal amounts of globulin and albumin, and the collection of these in a very milky fluid in the middle layer. Chloroform was added to the fluid as a preservative; after standing some weeks a fluid similar to the middle layer formed with ether was formed at the bottom of the fluid, which cleared slightly.

Milky-looking blood serum, differing from that in the lipaemia of diabetes in that it is not cleared by ether, occurs in many conditions, among which chronic parenchymatous nephritis is the most common. Such sera are probably of a similar nature to the milky ascitic fluids. In the case of a man in the London Hospital with chronic parenchymatous nephritis Dr. Panton found milky serum and, post-mortem, milky fluids in peritoneal and pericardial cavities.

In the case of a boy, Laurence C., aged 9, suffering from chronic parenchymatous nephritis, the serum was examined four times. On March 23, 1911, when recovering from an acute attack and being free from oedema, the milkiness of the serum was marked; on November 24, 1911, in an acute attack with marked oedema the milkiness was slight; and on December 15, the oedema being gone, the serum was quite clear. In October, 1912, during another acute attack with marked oedema the serum was very milky. Blood was withdrawn on this occasion from a vein; before the blood clotted the corpuscles sank to

the bottom; the clot formed four-fifths of the total bulk even after standing overnight.

The serum was not cleared by shaking with ether, nor by half saturation with ammonium sulphate (but no appreciable precipitate was formed); after adding caustic potash the fluid was cleared by extraction with ether.

From 5 c.c. of the whole blood about 2 per cent. of lipoid was extracted; on attempting to estimate the P_2O_5 in this by Neumann's method no precipitate was given with ammonium molybdate, showing that at any rate not more than a normal amount of phosphatide was present.

Micheli and Mattirolo (3) analysed the milky serum from two cases of chronic parenchymatous nephritis, thus:

	I.	II.
Sp. gr.	1016	1018
Coagulable protein . . .	4·6 %	7·3 %
Globulin	0·450 %	1·55 %
Lecithin	0·346 %	0·2383 %
Total lipoid	1·470 %	0·450 %

Both of these sera were peculiar in only containing small quantities of globulin. However, in both cases the serum was cleared by precipitation of the globulin by half saturation or dialysis.

The milkiness of these fluids is not like that due to proteins present as large molecules, for it is unaffected by altering the reaction of the fluid and by addition of salts in varying concentrations; and it is not carried down by the settling of fine particles (i. e. china clay and charcoal) added in suspension. It is therefore natural to attribute the milkiness to the presence of lipoid in spite of the fact that the fluids are not cleared by shaking with ether, and that in many which have been examined no globules of fat have been seen after staining with Scharlach R. The connexion with lipoid is also suggested in my second case by the collection of lipoid in the extremely milky gel formed by shaking with ether accompanied by the clearing of and removal of fat from the original fluid. Also by the fact that the serum examined was cleared by ether after adding caustic potash, and that lipoid was present in excess in the blood and in many milky ascitic fluids which have been reported.

In most of the fluids in which this point has been investigated the milkiness has had some connexion with the globulin present. Thus most fluids have been found to be cleared by precipitation of the globulin by half saturation with ammonium sulphate or other means. Micheli and Mattirolo found in numerous areas that this precipitate, after washing, redissolved to form a milky fluid.

However, the milkiness is not due simply to an excess of lipoid nor of any one kind of lipoid such as lecithin; the amounts of these vary extremely in the fluids which have been analysed: this is well shown by the following:

Author.	Total solids.	Coagulable protein.	Globulin.	Ether extract.	Lecithin.
Wallis and Scholberg (1)	4·844 %	2·006 %	0·693 %	1·501 %+[3]	0·0360 %+
,, ,,	2·520 %	0·652 %	—	0·814 %+[3]	0·274 %+[3]
Micheli and Mattirolo (3)	1·32 %	0·525 %	—	0·325 %	0·2185 %
,, ,,	2·10 %	1·57 %	0·17 %	0·141 %	0·0219 %
Fluid II above . . .	2·27 %	0·95 %	0·49 %	0·22 %	0·005 %
Micheli and Mattirolo (3)	3·349 %	—	—	0·01 %	—

The amount of lipoid and of lecithin is often no greater than that present in clear ascitic fluids, as is shown by the following:

Author.	Coagulable protein.	Globulin.	Lecithin.	Ether extract.
Micheli and Mattirolo (3)	5·9 %	2·6 %	0·13 %	0·190 %
,, ,,	1·62 %	0·19 %	0·0235 %	0·065 %
Marrack	3·08 %	1·81 %	0·06 %	0·144 %
,, ...	2·06 %	7·95 %	0·04 %	0·09 %

On account of the small quantities of lipoid often present and of the association with globulin mentioned above it has been assumed that in milky fluids a peculiar compound or physical association of globulin and lecithin is present. This is supported by an experiment of Joachim (2), who found that a milky ascitic fluid from a case of cirrhosis of the liver was cleared by half saturation with ammonium sulphate but not by one-third saturation; and that from the fraction precipitated by half saturation and not by one-third saturation, washed and reprecipitated, phosphatide amounting to 0·0363 per cent. of the original fluid could be extracted; while from the fraction obtained by one-third saturation none could be extracted. However, there is no reason to suppose that lecithin alone behaved thus; Joachim did not show that the other lipoid present or part of it was not similarly carried down by globulin. Nor is it necessary to assume any combination, but simply that the lipoid is carried down by the globulin; in fact, in my first fluid, in which little globulin was present, the milkiness was not removed by precipitating the globulin.

In fact the fluids bear a close resemblance to milk, which is not cleared by shaking with ether alone, but is cleared by ether after the addition of caustic potash. The resemblance is also shown by the following experiment: To 200 c.c. of a clear ascitic fluid 20 c.c. of milk were added (thus bringing the fat present up to about 0·3 per cent.) and the mixture stood for twenty-four hours; the resulting fluid was milky, not cleared by centrifugalizing nor by shaking with ether; it was cleared by half saturation with ammonium sulphate. The precipitate thus formed redissolved partly with water to form a milky fluid which was not cleared by centrifugalization. We may therefore assume that in these milky fluids some lipoid, not necessarily present in excess, is not in the usual state; possibly in clear fluids it is combined and in milky free.

The protein present seems to have some protecting action, preventing the extraction of the lipoid by shaking with ether. If the lipoid is present in great excess, as in three of Wallis and Scholberg's fluids, the protein is insufficient to

[3] In these fluids the lipoid was extracted by shaking with ether only.

prevent some from being extracted; also if the amount of protein present is very small the lipoid is unprotected. This is illustrated by a fluid observed by Dr. Panton from a case of heart failure, in which the fluid was completely cleared on shaking with ether; this fluid gave no precipitate on boiling with acetic acid. It is possible that the relation between the protein and lipoid is of the same kind as that in the stable gels formed by shaking a colloid solution with some fluid with which it will not mix, such as ether.

I take this opportunity of thanking Dr. Panton for his assistance and information concerning cases he has observed.

REFERENCES.

1. Bernert, *Arch. f. exp. Path. und Pharm.*, Leipzig, 1903, xlix. 32.
2. Joachim, *Münch. med. Wochenschr.*, 1903, l. 1915.
3. Micheli and Mattirolo, *Wiener klin. Wochenschr.*, 1900; and *Gaz. degli Ospedali*, 1901.
4. Wallis and Scholberg, *Quart. Journ. of Med.*, Oxford, 1909–10, iii. 301; *ibid.*, 1910–11, iv. 153.

CYSTICERCUS CELLULOSAE IN THE CENTRAL NERVOUS SYSTEM: WITH AN ACCOUNT OF TWO CASES

By RUPERT WATERHOUSE

With Plates 26 and 27

THE occurrence of cerebral symptoms in an individual harbouring cysticerci in his muscles or eye makes probable the presence of similar parasites in the brain.

This probability is increased if such symptoms are those known to be most commonly associated with the location of cysticerci in this situation, namely, epileptiform convulsions, headache, giddiness, mental disturbance, and vomiting. The detection at the same time of eosinophilia of the cerebro-spinal fluid will make the diagnosis practically certain, whilst in cases where no cysticerci have been discovered beneath the skin or within the eyeball an increase in the number of eosinophils in the circulating blood may be of use in directing attention to this rare but possible cause of anomalous cerebral symptoms.

Even when cerebral symptoms are associated with the presence of cysticerci in positions accessible to examination, if the number of the latter is small they may easily be overlooked and signs of intracranial disease be attributed to syphilis or some other cause, and should recovery occur, as it may, whilst, but not because, the patient is undergoing a course of antisyphilitic treatment this diagnosis is likely to be considered confirmed.

Though this may have happened in the past, at the present time the valuable test introduced by Wasserman would generally prevent such error, an error committed in the first instance in both cases about to be described.

Case 1. F. N., the son of a cabman, was born in 1876, in Bath. After leaving school he was employed as an errand boy until he was sixteen years old, when, giving his age as eighteen, he joined the Army. Till this time his health had been perfect.

In 1893 he had an attack of tonsillitis by which he was kept in bed one day. In 1894 he contracted gonorrhœa. In 1895 he went with his regiment to India, and in the following year and again later had further attacks of gonorrhœa. He is quite sure he never had a chancre or symptoms of syphilis, with the manifestations of which in the persons of his comrades he was quite familiar. In 1898 he had a 'fit' which was attributed to sunstroke. He had never had a fit before. About this time he remembers he suffered from tapeworm. Later he had two or three more fits before leaving India. In 1899 he had an attack of 'rheumatism', affecting first one wrist and then its fellow

but no other joints, and was in hospital six weeks; there was no gonorrhoea at the time. In 1901 he was in hospital six months with gonorrhoea and rheumatism in the knees and ankles. The same year he returned to England and two years later joined the Army Reserve. He had two or three fits each year after his return and was much troubled by 'rheumatism' in the feet and ankles, with at times pain in the right leg from the hip downwards. Eventually, in January, 1905, he was on this account admitted to the Royal Mineral Water Hospital, where he first came under my observation. At this time there was a good deal of swelling of the left tarsus and about the left ankle, whilst the right os calcis was enlarged in its upper and hinder part and the skin and soft parts around the tendo Achillis on this side thickened and tender. There was no cardiac disease and the temperature was normal. He underwent a course of hydrotherapeutic treatment, taking in addition ten grains of potassium iodide twice a day, and in five weeks' time, except that some thickening of the os calcis still remained, had recovered completely. He kept 'splendid' for the next twelve months, but on January 5, 1906, began again to have fits, which came on about every half-hour, each fit lasting some three minutes: the fits continued for the next three days, more occurring at night than in the daytime.

Through the night of January 9 fits, according to his mother's statement, occurred every five minutes, and on the following morning he was admitted to the Royal United Hospital under my care. His family history was as follows: His father, who used at times to take alcohol to excess, suffered much from gout in the feet and hands, and died at the age of 60 from 'dropsy'. His mother is living: in 1900 she had a 'seizure', which seems to have been an attack of facial paralysis only, three months after being knocked down by a bicycle. Two brothers, one of whom has been laid up with 'rheumatism', and one sister are living and well, and one brother died aged 14 days and one sister aged 3 months.

The history of his father's family is not known, but his mother's brother and three sisters are all very strong and well, having never known a day's illness, with the exception that one of the sisters had fits when a schoolgirl and was eventually sent to the county lunatic asylum, where she still remains. Apart from this there is no history of fits or insanity in the family. The patient himself was unmarried, and since his first fit in India had been a total abstainer.

On admission to hospital his state was as follows: A well-built, well-nourished, muscular labourer of medium height, he lay on his back, conscious but quite speechless. His head was of good shape, and there was no sign of injury or of tenderness of the scalp. His brow was mottled and bedewed with sweat. His ears were well formed but not symmetrical, the right standing out from the head more than its fellow. There was slight asymmetry of the face, accounted for partly by the effects of a blow on the nose when a child, of which the scar remained, partly by the absence of some teeth, and partly by facial paresis. The external auditory meatuses contained a little blood, but there were no signs of disease of the middle ear. His pupils, small medium, equal, reacted to light. There was no squint, no optic neuritis. He shut his eyes when told to, but the lid on the right side did not completely descend. His mouth was drawn to the left; the tongue could not be protruded. His teeth were irregular in size, shape, and setting, and his palate, too, lofty and rather V-shaped. There was complete flaccid paralysis of the right arm and leg. The radial reflexes could not be obtained; the triceps jerks were present. The epigastric reflexes were present, the abdominal could not be obtained. The cremasteric was present on the left, not obtained on the right. Stimulation of the outer side of the sole of the foot caused on the right side dorsiflexion of the great toe and contraction of the tensor fasciae femoris, and on the left side contraction of the tensor fasciae femoris and dorsiflexion of the ankle. When first seen the knee-jerk

was present on the right, absent on the left, but a few hours later could not be obtained on either side.

His temperature was 101° F. Pulse 96. Respirations 28. The urine was acid, specific gravity 1032, thick with amorphous urates, and contained neither albumin, sugar, nor casts.

Ten grains of potassium iodide and twenty of potassium bromide were administered on his admission to hospital at 4.30 p.m. In the following two and a half hours he had, at fairly regular intervals, twenty-one fits. At 6.30 p.m. the following note was made: T. 102°, P. 100, R. 24.

'Between the fits he lies quietly on his back with the left leg drawn up, the left hand across the chest, and the elbow away from the side. Face flushed and sweating profusely. Unable to speak, he no longer understands what is said to him. The pupils are small medium and equal; no squint. The right palpebral fissure is slightly wider than the left. Each fit commences by the eyes moving slowly in a series of jerks to the right side, the face at the same time turning slowly to the right. Next the right side of the face is screwed up, the brow wrinkled, and the eyes turn to the left, the face remaining turned to the right. Spasmodic movements of the right arm then begin and, to a much less extent, affect the left, the legs become extended and rigid, and general clonic convulsion, affecting the right side more than the left, follows. The tonic stage lasts from five to ten seconds, the clonic sixty seconds. In the fits he becomes very cyanosed and sweats profusely all over. Mucus collects at the back of the throat, causing him, when the fit is over, to cough, but without completely clearing the throat.'

The last fit occurred at 2.30 a.m. on the 11th, the total number of fits in the ten hours following admission being fifty-four.

At 10 a.m. he looked decidedly better, but seemed sleepy, 'not flushed or sweating. Hears what is said to him but does not appear to understand, since he does not perform various simple acts when requested to. Draws up both legs to-day. Right arm still paralysed, but not so flaccid as yesterday. Reflexes as before. In the evening when told to shut his eyes he opened his mouth. T. 100·6°, P. 80, R. 24.' He slept well through the night and on the following morning would shut his eyes, protrude his tongue, clench his fist, &c., when requested. When asked if his name was Smith, Robinson, &c., he took no notice till his own name was mentioned, when he nodded his head. 'Right eyelid does not completely close, and there is paresis of the right side of the mouth. Right arm completely paralysed and movement of the shoulder-joint seems to give him pain; no sign of dislocation or fracture. Both knee-jerks obtained, but there is a more vigorous response on the right than on the left. "Babinski" right; dorsi-flexion of ankle left.'

At this visit for the first time were observed a number of 'subcutaneous nodules', whose true nature was not appreciated at the time, but which later proved to be cysticerci. Each was firm, elastic, globular or oval, and about the size of a large pea. The skin over them was freely movable and they themselves could be readily moved to and fro over a short distance. Their position is indicated in the accompanying diagram. (See Fig. 1.)

'January 13. Has had a fairly good night; less drowsy to-day. Said "yes" last night. Protrudes tongue freely and it does not deviate to either side. Understands everything said to him. Still complete paralysis of right arm and pain when shoulder is moved. Can draw up right leg; plantar reflexes as before. Bowels well opened after an enema for the first time since admission, notwithstanding doses of calomel and croton oil and glycerin suppositories and enemata.

'January 14. Better. Has said "yes" and several short sentences. There is crepitus (?joint) on movement of right shoulder.

'January 15. No traces of facial paralysis remain. Can move right arm a little.

Still crepitus (? bony) right shoulder and girth of shoulder one inch greater than that of the opposite side. Acromiocondylar measurements equal.'

My surgical colleague kindly saw the man with me and came to the conclusion that there was an intracapsular fracture of the humerus.

During the next few days steady improvement in every respect took place. He slept a great deal and very soundly. The grasp of the right hand became stronger and pain on movement of the shoulder less.

On January 22 he was taken to the X-ray department, where it was found that the head of the humerus was in the natural position and that there was no evidence of fracture.

'January 29. Very much better. Has noticed some numbness and twitching in the right forearm for the last day or two; this he had noticed too at times before the present series of fits. No optic neuritis. His shoulder quickly recovered, and on February 5 he left hospital apparently quite well.'

The treatment adopted during his stay in hospital was as follows: On admission 10 gr. of iodide and 20 gr. of bromide of potassium were prescribed to be taken every four hours. Two hours later 2 gr. of calomel and a minim of croton oil were administered. Hypodermic injection of $\frac{1}{6}$ gr. of morphine sulphate and inhalation of amyl nitrite had no effect whatever on the fits, so the amount of potassium bromide was doubled and 10 gr. of chloral hydrate were added to the mixture. Twelve hours after admission, the fits having ceased two hours, the amount of his mixture was diminished by one-half. On January 15 the amount of chloral and potassium bromide was again halved, and on the 29th the chloral was entirely omitted.

As an out-patient he continued to take 10 gr. of potassium bromide and 5 of potassium iodide three times daily until May 1, when he had a slight fit. His mixture was changed to one containing 1 fl. dr. of solution of perchloride of mercury and 5 gr. of potassium iodide in a fluid ounce of infusion of quassia, which he continued to take until the end of May. On June 20 he said that since ceasing to take the medicine he had once or twice noticed flashes of light above and outside the right eye, and at times his right arm 'moved of itself'. The general health was very good, 'better than for years.' No changes in the fundi were found.

He kept quite well, taking no drugs, until April, 1907, when he had a slight 'attack' without loss of consciousness. This began by his tongue cleaving to the roof of his mouth; he tried to tell his mother to put something between his teeth but found he could not speak, his mouth twitched, his head turned to the right, and his limbs became stiff, of all of which he was himself cognizant. Examination of his nervous system revealed no abnormal physical signs. He again took perchloride of mercury and iodide of potassium, which was continued until the middle of July. Towards the end of September he was, for two or three days, annoyed by attacks, each lasting about five minutes, of twitching of the right side of the mouth and face, during which he was unable to speak but did not lose consciousness. Shortly afterwards he had an attack in which he did lose consciousness, and following this 'strange feelings' at times for about a fortnight. He again took the mixture mentioned above until January, 1908. After this he kept well until March, when he had a 'cold', and following this a slight nocturnal attack which left some pain in the right shoulder. On the evening of April 6 he had another fit, which he felt coming on, so that he was able to call his mother before becoming insensible.

A careful examination at this time led to the discovery that the 'nodules' previously present in the subcutaneous tissue occupied different sites to those in which they were first found. (See Fig. 1.)

That over the left breast was excised under eucaine. Globular in shape, its diameter was a quarter of an inch. It consisted of an outer fibrous wall enclosing, free within its cavity, which was almost filled thereby, a second smaller cyst with

a delicate transparent wall and containing within it a clear watery fluid and at one spot a nipple-like conical projection about one-eighth of an inch in length. Microscopically this presented the appearance of Cysticercus cellulosae. (See Plate 26.) From this time till March, 1911, he took a mixture containing 10 gr. of each of the bromides of potassium, sodium, and ammonium twice a day.

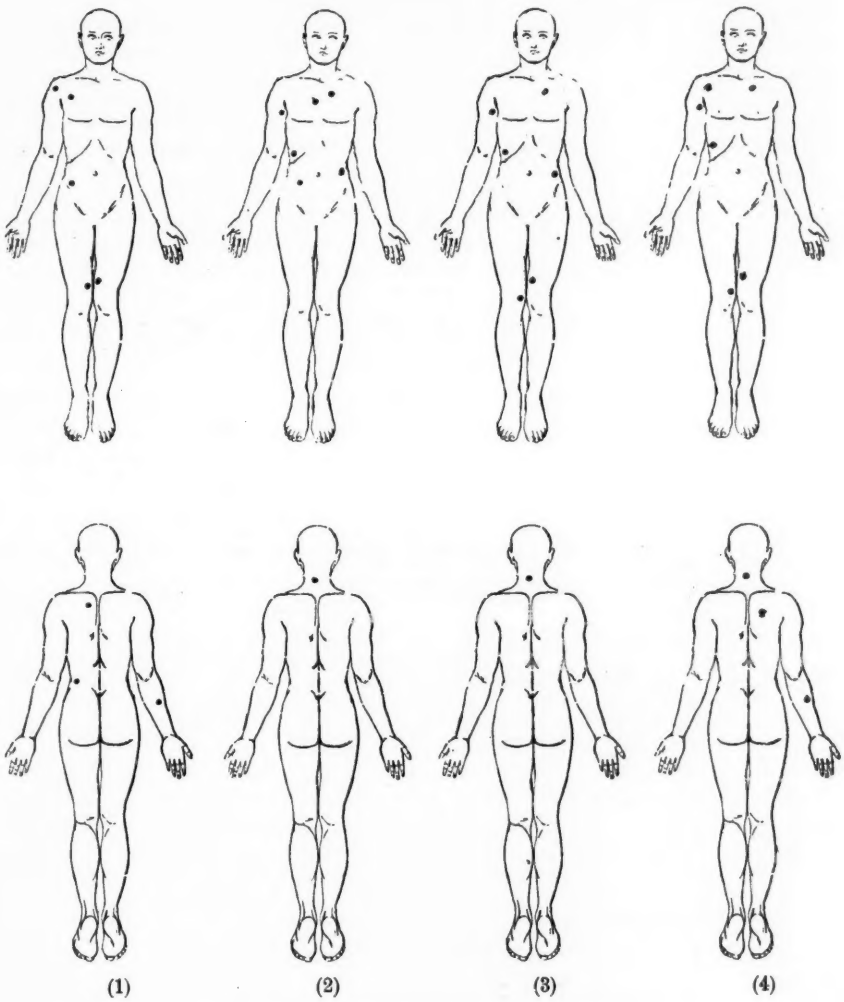


FIG. 1. To show situation of cysticerci in Case 1.
(1) On January 12, 1906. (2) On April 17, 1908.
(3) On January 5, 1911 (all much smaller). (4) On November 5, 1912 (all very minute).

In November, 1909, following a severe 'cold', an acute arthritis of the left sterno-clavicular joint developed. The left arm was kept at rest and the painful joint painted with tincture of iodine, whilst a mixture containing sodium salicylate and potassium iodide was administered internally. Four or five days

later little or no relief had been afforded, and the severe pain was causing him to look very ill. The mixture was changed to one containing 10 gr. of urotropin and rapid recovery ensued. There was no evidence of gonorrhoea or gleet at this time, nor any symptom suggesting stricture of the urethra.

During 1910 he kept very well, except that one night in June he bit his tongue in his sleep, and one day in December, whilst in church, observed 'flashes of light', so that, thinking a fit was imminent, he came out.

On March 1, 1911, the cyst at the nape of the neck, not more than one-third its size of four years before, was removed. It was found to be situated deeper in the tissues than had been anticipated and was as large as an ordinary pea. It consisted of a firm outer fibrous wall which, when opened, disclosed a smaller body lying free within. This inner cyst, the wall of which was thickened, pulpy, and opaque, contained no fluid, but at one spot on its inner surface was a tiny elevation not more than one-quarter the size of an ordinary pin's head. Microscopical sections were made of this, and one showed plainly two suckers with the ring of pigment granules round the base of the rostellum and the remains of a hooklet. From March, 1911, to the present time the patient has continued to take 30 gr. of bromide every morning and has had no more fits.

On November 5, 1912, little hard movable bodies no larger than millet seeds could, with difficulty, be detected in the positions denoted in Fig. 4.

Since 1906 he has worked as an outdoor labourer on the golf links.

Examinations of the blood were made as follows:

1911.	Total Leucocytes.	Polymorpho-nuclears.	Lympho-cytes.	Mono-nuclears.	Baso-phils.	Eosino-phils.	Eos. %
Mar. 2	—	66 %	27 %	4 %	1 %	2 %	2·0
Mar. 6	7,600	4,700	2,500	228	25	76	1·0
1912.							
June 24	6,300	3,600	2,240	220	—	240	3·8
July 1	6,200	3,980	1,740	260	—	220	3·5
July 9	6,200	4,440	1,400	140	—	220	3·5
Sept. 28	6,200	3,740	1,980	320	40	120	2·0

Summary of Case 1.

1898. Suffered from tapeworm. About the same time had a fit followed by two or three fits every year until
1905, when he had no fits.
1906. Status epilepticus leaving him aphasic and hemiplegic for a week. Cysticerci in muscles well developed. No more fits until
1907, when he had one major and two or three minor attacks.
1908. Two fits. Cysticerci still well developed.
1909. No fits.
1910. One doubtful (nocturnal).
1911. No fits. Cysticerci shrunken.
1912. No fits.

There can be little doubt that the cerebral symptoms in this patient were due to the presence of cysticerci in the brain.

They commenced at a time when the patient was the host of a tapeworm; they attained a climax when the cysts in the muscles were at the height of their development; they disappeared coincidently with the retrogression of these cysts; and, finally, the form they assumed was what has been most commonly observed

in other cases of this kind, namely, epileptiform convulsions differing from true epilepsy in the more gradual onset of the fits.

The time required for the development of the cysticercus is two and a half months, and the duration of its life, according to Stich's observations of cysticerci under the skin, amounts to from three to six years. 'They then die and undergo retrograde metamorphosis.' F. N. suffered from tapeworm and his first fit in 1898, and *ten* years later the cysticerci in the muscles had not begun to diminish in size, though afterwards they rapidly dwindled. Assuming, then, the cause of the fits to be invasion of his brain by cysticerci, we must suppose either that those in the muscles were a later crop, or else that the cysts do not necessarily begin to shrink until some time after the death of the parasite, or, finally, that the life of the animal may at times be longer than that mentioned.[1]

That epilepsy originated by cysticerci in the brain may continue after retrogression of the parasites is only what is to be expected on general grounds, and Henneberg records two cases illustrating this: the first that of a man aged 26 who had been epileptic since the age of 13, and at whose autopsy a dead and calcified cysticercus was discovered in the right temporal lobe; the other that of a man who suffered from epilepsy from the age of 31 till his death twenty-three years later, and in whose brain several bladderworms were found, some the size of millet seeds, some as large as hazel nuts, one the size of a large cherry, and one that of a large bean.

The long interval that has elapsed since my patient's last fit leads one to hope that in him the epileptic 'habit' has not become established.

In the next case the diagnosis was confirmed by examination of the brain after death.

Case 2. J. W., born in 1882, in Wiltshire. At the age of 8 had an attack of chicken-pox, but remembered no other illness during his youth. He worked as a farm-labourer till 1900, when he enlisted in the Army. From 1901 to 1903 he served in South Africa, and from 1903 to 1908 in India. When at Amballa he was laid up three weeks with malarial fever, but had no other sickness whilst abroad. He had not been a very heavy drinker or smoker, had never had any form of venereal disease, and neither he nor any of his relatives ever had tapeworm. He was unmarried; his parents were alive and well; he was the fourth of five children, and his two brothers and two sisters were living and healthy. None of his relations ever had fits.

Shortly after his return from India he was laid up a month with malaria.

In the summer of 1909, whilst working again as a farm-labourer, he had four fits. He had never had fits before, and on August 5 came to the out-patient department of the Royal United Hospital.

A well-built, muscular man; he was, however, noticeably anaemic. There was no optic neuritis, no signs of plumbism, no albuminuria. He had suffered from neither headache nor vomiting, but said that at times he was seized with giddiness. A mixture containing Ferri et Ammon. Cit. gr. iv, Pot. Brom. gr. xv, Liq. Hydrarg. Perchlor. ℥j, Pot. Iod. gr. v, Decoct. Cinchonae ℥j, was prescribed to be taken three times a day.

[1] The last of these suppositions is the most probable, and indeed 'there is at least one recorded case in which a living cysticercus located in the eye was under observation during twenty years' (Allbutt and Rolleston).

He quickly regained a normal colour and the fits ceased.

After taking the above mixture for three months he discontinued his attendance and remained perfectly well until nine months later, when he received a blow on the back of the head. He kept at work for a week, but was then obliged to give up in consequence of headache; about the same time he began to 'see double'. Two months later vomiting, especially on rising in the morning, set in. On November 3, 1910, he came again to the hospital and was at once admitted as an in-patient under Dr. Wilson-Smith.

On admission he was complaining of almost continual headache, chiefly, he said, behind the eyes. His pupils were equal (sometimes the right was slightly the larger), circular, and reacted to light and on convergence. There was some photophobia. There was diplopia on looking to the right and distinct paresis of the right external and less of the left internal rectus. There was well-marked double optic neuritis. No nystagmus. He could not open the left eye against pressure quite so well as the right. His vision was $R = \frac{6}{6}$, $L = \frac{6}{9}$. All the other cranial nerves were normal. His muscular power was good and there was no muscular atrophy. No Rombergism. Gait natural. Sensation normal. No trophic or vasomotor changes. All the superficial and deep reflexes normal with the exception of the abdominal, which were more brisk on the left than on the right. Plantar reflexes flexor. Temperature, pulse, respirations normal.

Urine S. G. 1026, no albumin or sugar. Weight 10 st. $4\frac{1}{2}$ lb. There were three small circular scars about half an inch in diameter on the lower part of the right shin.

Inunctions of ung. hydrargyri were given daily, and 20 gr. of sodium iodine every four hours.

Headache continued to be very severe, and phenazone, aspirin, and various forms of counter-irritation were employed without affording much relief.

On November 8 Mr. W. M. Beaumont kindly examined the eyes and estimated the amount of swelling of the right disk at $1\frac{1}{2}$ mm. and that of the left at $1\frac{2}{3}$ mm.; from the appearance of the white patches he was inclined to the view that the papilloedema was of longer standing in the left eye than in the right.

On the same day the patient's temperature rose to 101·4° F. and continued to range between 99° and 102° till November 10, when the iodide was discontinued. On the same evening lumbar puncture was performed. The fluid withdrawn was clear and natural in appearance and was not under increased tension. On centrifugalization a deposit was obtained which microscopical examination showed to consist of leucocytes, a count of 300 stained (Leishman) cells showing 200 lymphocytes, 97 eosinophils, and 3 polymorphonuclears.

A more minute examination of the patient led to the discovery of several small, firm, globular bodies, neither painful nor tender, apparently deep in the subcutaneous tissue in the positions indicated in Fig. 2. Most of these were the size of small peas, but the largest was the size of a small cherry and was removed under eucaine. It presented the typical appearance, naked eye and microscopical, of Cysticercus cellulosae enclosed in a firm fibrous capsule, to the outer surface of which a few muscle fibres still adhered. On the following day, November 11, his headache was less, and from this time steadily decreased. On November 12 sodium iodide was again given in doses of 10 gr. three times a day, increased on November 15 to gr. xv, and on November 24 to gr. xx.

About this time the optic neuritis began to subside, and in January, 1911, had completely disappeared. Naked-eye and microscopical examinations of the stools failed to reveal any evidence of tapeworm even after the administration on different occasions of a drachm of liquid extract of male fern and 4 oz. of infusion of kousso, the bowel being emptied as far as possible first.

January 4. Another fit, the twitching affecting the left side only. January 9. Mercurial inunctions discontinued. January 11. Very severe headache all day; in the evening an attack of shivering without rise of temperature; vomited

twice. January 12. Another fit, left side only at first, then general; mercurial inunctions resumed. Another fit on February 3, and again on February 4, twitching affecting both sides, but chiefly the left.

His general condition remained much the same until March 21, when he was discharged. His weight was 11 st. 4½ lb. A fortnight later he was readmitted, and 7 minims of liquid extract of male fern in a mixture were prescribed to be taken three times a day. On the following day he had another fit, the first since February 24.

April 10. Optic disks pale, otherwise normal. April 17. Sclerotics slightly yellow. April 20. The jaundiced hue of the sclerotics and skin more marked; no bile pigment in urine; filix mas was omitted for two days.

April 23. Complained of sudden very severe pain in the head and shivered a great deal; did not feel cold; no rise of temperature; felt as if he was going to have a fit. One-fifth of a grain of morphine was administered hypodermically and this feeling passed off, but he continued to feel sick and unwell until fourteen hours after the inception of these symptoms, when another fit occurred.

He complained that he always had headache after taking the mixture, so this was again discontinued and perchloride of mercury and iodide administered. May 3. Another cyst appeared over the inner side of the head of the left tibia, preceded by a pricking sensation. Seven minims of male fern, this time in capsules, was again ordered three times a day. May 5. Complained of sleeplessness and headache.

May 6. Another fit; shouted and threw his limbs about; remembered nothing of it afterwards. May 13. Sclerotics again yellow; headache, shivering, and nausea; male fern stopped and calomel gr. ii and copious draughts of water given. May 31. Optic disks appear normal.

June 14. An ounce of castor oil followed by liquid extract of male fern, m. 90, and later by another dose of castor oil. No signs of tapeworm in stools. Another fit.

June 28. Two fits; knew they were coming on; vomited after first; very drowsy since. June 30. Two fits. July 6. No optic neuritis. July 7. For two days has been much troubled by flashes of light—like stars—above and to the right. July 14. Two oz. of mist. alba were given at night, and the following morning half this prescription: Infusion of Pomegranate Root ℥j, Pumpkin Seeds ℥j, Powdered Ergot ʒj, Boiling water ℥x, mixed with Ethereal Extract of Male Fern ʒj, Croton Oil m. ii in Emulsion ℥j. A week later the other half was taken, but on neither occasion were there any signs of tapeworm.

On July 29 he was discharged. He then attended as an out-patient and took 15 gr. of potassium bromide three times a day.

In August he had two fits. In February, 1912, he had a slight fit, and at this time fresh cysts were observed over the shoulders and in the front of the neck. In April the cysticerci were all much smaller and his general condition better, but the same month he had another fit, and in June three. He still suffered at times from headache and giddiness. 'Specks in the eyes' troubled him, especially in bright sunlight. There was still diplopia and he found particular discomfort from vertigo on stooping, though other sudden movements of the head did not occasion this.

In July his general health was better, but he was still unable to work, complained of headache at times and sleeplessness. In August he had two fits and slight pain at the top of the head and behind the eyes 'all the time'; sleeping well.

He was last seen alive by me on September 28, when his condition was much the same.

For the details of his final illness I am indebted to Dr. Philip Jones of Coleford, who writes as follows:

'J. W. came down to my surgery on Friday evening, October 11, very

unsteady and rather incoherent of speech. His respirations were constantly interrupted by a short dry cough, but were between 30 and 40 per min. and the pulse 120; the temperature 100·4°. He complained of pain in the chest low down. I found there was a patch of pneumonia with pleurisy, and sent him straight home to bed. Temperature next morning, October 12, 101°; respirations and pulse much the same. Sputum "rusty" and thick. The pneumonic patch had spread and there was still a good deal of pain. He was taking nourishment well; very constipated, but Pulv. Jalapae c. Cal. acted well. Coming back one night between 6 and 7 I looked in on him and found evening temperature 102°, and I don't think it ever rose above this.

Morning of October 16 he was comatose. They told me they could not get him to take anything after midnight and that he lay with his teeth tightly clenched. He remained like this until his death at 3 a.m. on October 18.'

Examinations of this patient's blood gave the following results:

1911.	Total Leucocytes.	Polymorpho-nuclears.	Lympho-cytes.	Mono-nuclears.	Baso-phils.	Eosino-phils.	Eos. %
Jan. 18	6,500	4,300	1,700	—	—	580	8·4
Feb. 20	10,700	7,000	2,200	480	—	770	7·2
Mar. 4	6,400	3,540	1,900	310	20	630	9·8
Mar. 14	7,800	3,200	3,400	280	46	870	11·1
Mar. 27	8,400	5,100	2,260	340	20	780	9·2
Apr. 11	9,400	6,160	2,460	280	—	500	5·3
May 10	13,000	8,500	3,250	500	25	750	5·7
June 10	10,500	6,400	3,300	200	70	470	4·5
July 27	7,600	5,140	1,760	280	—	380	5·0
1912.							
Apr. 4	9,900	7,470	1,410	—	30	390	3·9
June 6	9,000	6,460	2,420	—	—	120	1·3
July 4	8,700	7,100	1,440	—	20	140	1·9
Sept. 28	13,000	9,900	2,600	130	—	330	2·5

Summary of Case 2.

No history of tapeworm.

1909. Four fits; giddiness; anaemia. Recovery; good health for nine months.

1910. Fits; vomiting; giddiness; headache; optic neuritis; diplopia. Cysticerci in muscles. Eosinophilia of blood and cerebro-spinal fluid.

1911. Optic neuritis gone; headache much less; no more vomiting; still diplopia, some headache, and fits.

1912. Occasional fits; incapable of work; death from meningitis following acute pneumonia.

An examination of the body was made thirty-six hours after death.

There was pneumonic consolidation of the lower lobe of the right lung with recent adhesions to the chest wall and fibrinous exudate between the middle and lower lobes, and a few recent adhesions between the lower lobe of the left lung and the diaphragm.

Several cysticerci were discovered in the pectoral muscles and in the recti abdominis, a group of three or four in the left ilio-psoas, one projecting into the lower part of the left pleural cavity, apparently in the intercostal muscle of the tenth space, and one in the right half of the diaphragm. The latter was collapsed and opaque looking, but there was no evidence that it had ruptured into the pleural cavity and no sign of inflammation immediately around it. The others were all tense cysts, mostly oval, with the long axis lying parallel to the

muscle fibres, and varying in size from that of a pea to that of a small olive. Each contained a scolex retracted within its cavity and each was surrounded by an adventitious fibrous capsule.

The skull-cap was of normal thickness, and the outer surface of the dura mater appeared natural and was easily separated from the bone. There was

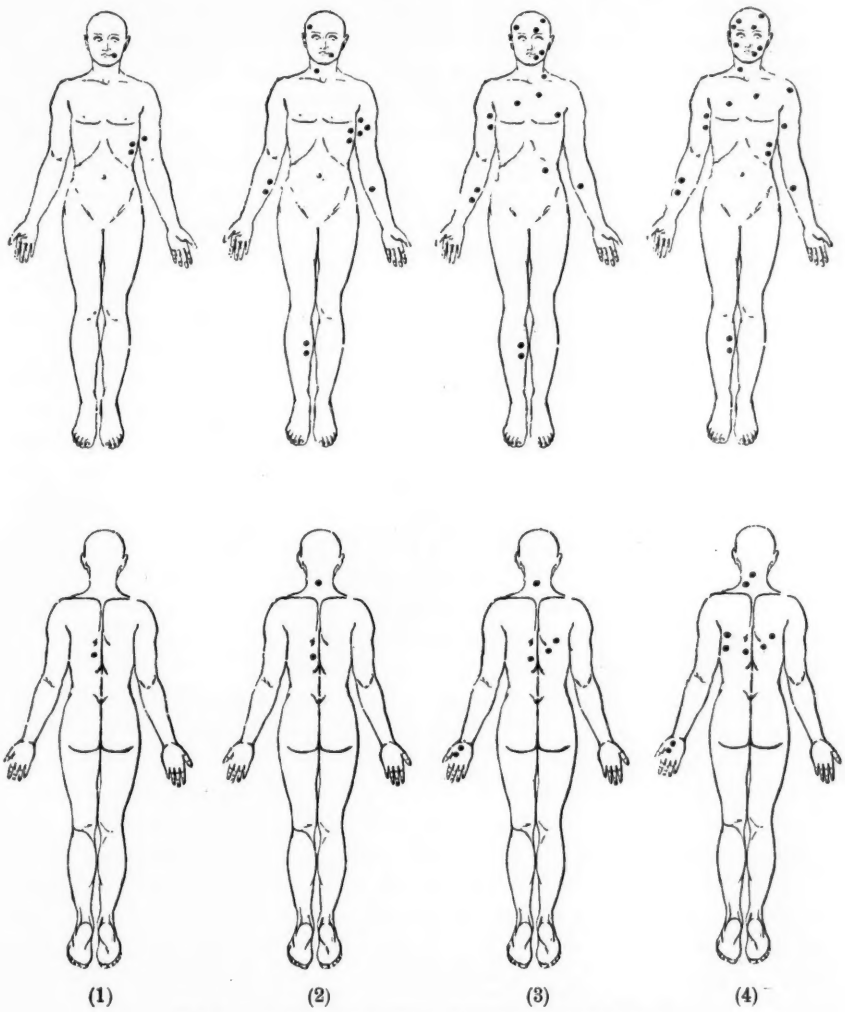


FIG. 2. To show the position of the cysticerci in Case 2.
(1) On November 12, 1910.
(2) On December 22, 1910.
(3) On January 4, 1911.
(4) On March 3, 1911.

no marked increase of cerebro-spinal fluid. Seven cysts, each about ¼ inch in diameter and each firmly attached to the dura, were found in the sub-dural space, four being connected with the upper surface of the tentorium on the left side, one near the apex of the left petrous bone, and one in the right anterior

fossa. The brain showed some greenish lymph in the meshes of the pia-arachnoid in the sulci of the vertex and contained between two and three hundred cysts. The vast majority of these were situated in the cortex, some projecting slightly above the surface under the pia mater, others being in the deeper parts of the grey matter. Two were situated in the corona radiata, one

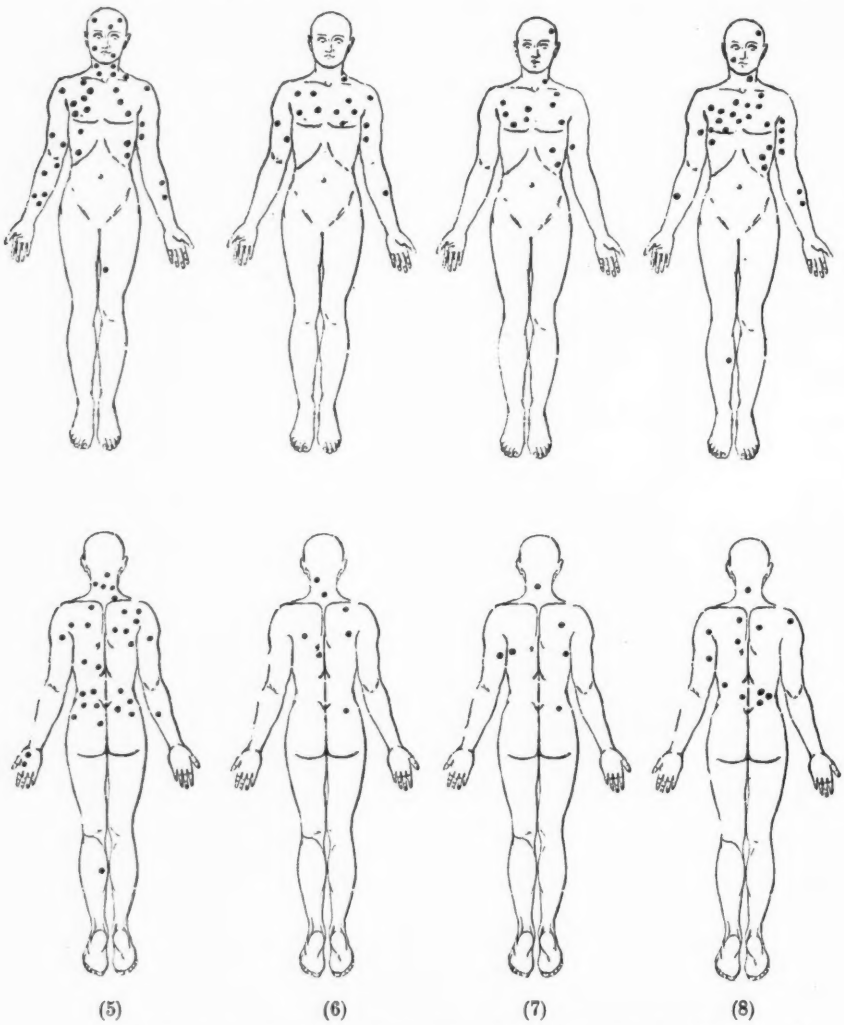


FIG. 2—*continued.* To show the position of the cysticerci in Case 2.

(5) On August 17, 1911.
(6) On June 6, 1912.
(7) On July 11, 1912.
(8) On September 30, 1912.

in the right optic thalamus, two in the left, seven in the right corpus striatum, five in the left, two near the surface of the left lobe of the cerebellum, one deeply placed in the substance of the right, one in the third ventricle, and one in the fourth. (See Plate 27.)

An interesting feature in both these cases was the apparent change of position of the parasites in the muscles at different times (see Figs. 1 and 2). This, though observed in the first, was particularly noticeable in the second case, where cysts made their appearance in fresh localities over a period of several months. Thus the two cysts felt on the inner side of the skin at the beginning of 1911 could no longer be felt in August of that year, nor in June or July of the next, though one of them was easily demonstrable in the following September. A particularly careful search for those felt in January, March, and August, 1911, in the muscles between the thumb and forefinger was made in June, July, and September, 1912, with negative result, but Dr. Jones tells me that a week before his fatal illness the patient called to show him some 'fresh lumps' in his hand which, there is very little doubt, were those which had been felt on previous occasions.

At the time it was thought that fresh cysts making their appearance over so long an interval indicated fresh crops of cysticerci, hence persevering efforts were made to destroy a hypothetical tapeworm in the man's bowel, but this explanation falls to the ground in the absence of any such source of reinfection. Another possibility is the unlikely one that the parasites continue to change their situation even after reaching the size of a pea or larger. Thus Leuckart says, 'The young worm by no means always remains in its first habitat; it frequently commences to move from it, even though slowly still always perceptibly.... Young Coenurae have been seen to form long tracks and passages covered with exudate on the surface of the brain.' The same happens, he says, with cysticerci in the liver and lungs, which are continually forcing their way outwards, and thus gain access to the cavities of the body.

Pye-Smith records the case of a soldier, aged 30, who had been six years in India and Burmah. In June, 1891, he was in Guy's Hospital with influenza followed by neuralgic headache. Whilst in hospital he noticed a lump on the left arm, and after his discharge in July noticed others. Fifty were counted on the face, trunk, neck, and limbs. In April, 1892, he was readmitted. 'In the first week of his stay in the ward several new ones appeared rapidly, one in the ball of his thumb.' Two were removed and proved to be Cysticerci cellulosae.

This question of the possibility of the migration of the parasites is discussed by Mosler and Peiper, who say that the cysticercus possesses the means of active locomotion in the presence of organic musculature in the neck or caudal vesicle, but come to the conclusion that 'whether fully formed encapsulated cysticerci of relatively large circumference can effect any change of locality does and must appear to be doubtful'. Another possibility is that after the cyst has attained a size sufficient to render it easily palpable the tension within it may at times be so diminished that it can no longer be detected.

In the eye several observers have seen with the ophthalmoscope the parasite alternately invaginate and protrude its head and grope in this or that direction as though seeking a spot to commence sucking at. If a bladderworm deep in a muscle managed to protrude its head in this way it is quite likely that

it would no longer be palpable, though how this could occur after encapsulation it is difficult to understand.

In the case of older cysts it may be that, though easily felt when distended with fluid, they may disappear with the death of the parasite and collapse of the cyst, to reappear only with the deposition of lime salts in the worm's remains.

In Case 2 the pronounced eosinophilia of the cerebro-spinal fluid was of value in serving to clinch the diagnosis that the cerebral symptoms depended upon parasites in the central nervous system similar to those in the muscles.

In the comparatively small number of cases in which observations of the cerebro-spinal fluid in this disease are recorded, no mention of the eosinophil cells is made.

In a case of Chotzen's in which after death cysticerci were found at the apex of the temporal lobe, at the base of the brain, and in the third and fourth ventricles, lumbar puncture was performed twice, and on each occasion the pressure of the fluid was slight and there was lymphocytosis and increase of albumin.

Henneberg also found lymphocytosis without increase of pressure in the cerebro-spinal fluid of a pregnant woman who died comatose after headache, vomiting, optic neuritis, giddiness, paresis of sixth, seventh, and twelfth nerves, &c., and in whom a calcified cysticercus was found in the right optic thalamus.

The same author relates another case, that of a man, aged 38, in whom were found at autopsy a cysticercus free in the fourth ventricle and two in the cauda equina.

On each of the two occasions on which lumbar puncture was performed the pressure of the fluid was 180 mm. On the first occasion 6 c.c. of clear fluid were withdrawn, containing somewhat over 1 per cent. of albumin (Nissl) and no cellular constituents.

Stern records four cases in each of which death was due to a cysticercus in the fourth ventricle, and in two of them lumbar puncture was performed. In the first case, on one occasion the fluid contained lymphocytes and erythocytes and on another there were numerous 'leucocytes' in the sediment without increase of the albumin content. In the other case lumbar puncture was performed twice, but particulars of the condition of the fluid are not forthcoming.

The blood findings in Case 2 are not without interest. It will be observed that the eosinophilia remained fairly steady at about 9 per cent. during the first three months of 1911, and that after treatment with male fern a rather abrupt fall to 5 per cent. took place. If the total number of eosinophils in the blood is taken into account, however, this fall is found to be apparent rather than real, and certainly no improvement clinically ensued from treatment which, on the contrary, appeared but to increase the patient's distress.

Treatment in this way, by small repeated doses of male fern, was instituted by De Renzi in 1908. A man, aged 38, passed tapeworm segments five years before. Three years later he had two convulsions. Taenia solium with head intact was expelled by a vermifuge. Nevertheless the convulsions became more severe and were accompanied by general prostration, vertigo, palpitation, and

shortness of breath. There were numerous subcutaneous cysticerci, one of which was removed. There was besides 'une éosinophilie accentuée'. Two to four capsules of male fern were taken each day for some time, and the cerebral troubles, subcutaneous cysticerci and eosinophilia, quickly disappeared.

Dianoux, who mentions that since the above De Renzi has successfully treated two other cases of cysticerci in this way, relates the case of a man, aged 31, who for some months suffered from epileptiform fits, headache, and diminution of vision in the left eye, and in whom cysticerci were present in the vitreous humour and thigh. Taenia solium was expelled after a vermifuge. 50 centigrammes of extract of male fern were given three or four times a day for seventy-one days, with interruptions. In all 102 grm. were taken. Both cysticerci disappeared in seven weeks, and five months later there had been no more fits.

In consequence of the above cases Moussu has tried the effect of similar treatment in sheep affected with Cysticerci coenurae and in a measly pig, and comes to the conclusion that male fern administered in this way will arrest the development of cysticerci, but that it has no effect on the fully grown parasites.

On both occasions on which treatment of this kind was administered to my patient his skin and sclerotics after a few days became greenish yellow, and it was thought he was jaundiced. As at no time, however, could any bile pigment be detected in the urine, it is probable that his yellow hue resulted from some other colouring matter.

Reports of cases of cysticerci in the central nervous system are not so uncommon in continental, and especially German and Italian, literature (Stern was able in 1907 to collect seventy-two instances of cysticerci in the fourth ventricle, including four of his own). The number of cases in English periodicals is, however, small, and it has been thought well to append a brief abstract of them. The nature of the cysts in some of the earlier cases is open to question.

1. *Dagleish*, 1831. ♂ 27. Headache: rigors: vomiting: sudden death. 'Hydatid' in 4th ventricle.

2. *Tanner*, 1843. Fits. 'Hydatid' immediately anterior to corpora quadrigemina.

3. *Ottley*, 1844. ♀ 40. Headache: giddiness: confusion: hemiparesis: fits. Numerous cysts in pia mater and convolutions.

4. *Stewart*, 1848. Case 1. No symptoms. Cysts in pia mater, corpus striatum, and cerebrum.

Case 2. Fits. Cysts in pia mater and in substance of cerebrum and cerebellum.

5. *Hulke* (quoted by Cobbold, 1855). Fits. Numerous cysts in brain near surface.

6. *Brittain*, 1859. ♀ 29. Vomiting: headache: excitement. Cyst in 4th ventricle.

7. *Burgiss*, 1862. ♂ 39. Headache: cranial nerve paisies: recovery.

8. *Burton*, 1862. ♀ 20. Vomiting: headache: fever: fits. 'Hydatid' in right crus and cerebellum.

9. *Harley*, 1867. ♀ 15. Headache: somnolence. Cyst in right corpus striatum.

10. *Andrew*, 1870. ♂ 32. Vomiting: pain back of neck: inability to use legs: slight convulsion: coma. Cysticercus in 4th ventricle.

11. *Flint*, 1881. ♂ 17. Headache: vomiting: coma. Cyst in left lateral ventricle.

12. *Gulliver*, 1886. 53. Cirrhosis of liver. Status epilepticus—death in 12 hours. Cysticerci in pia mater, cerebral cortex, and pons.

13. *Brittain*, 1881. ♀ 16. Headache: vomiting: fits. Cyst in lateral ventricle.

14. *Carr*, 1890. ♂ 28. Headache: drowsiness: fit. About forty cysts scattered through cerebrum.

15. *Black*, 1903. ♂. Mania: paralysis: fits. Hundreds of cysticerci in pia mater and hemispheres: five in 4th ventricle.

16. *Conry* (reported by Black, 1903). ♂. Dementia: fits. Cysts in cerebrum and cerebellum.

17. *Sullivan*, 1903. ♂ 27. Fit followed by hemiparesis for two days: headache: rigors: blindness: fits: otorrhoea the sediment of which contained taenia hooklets. Cysts in pia mater.

My thanks are due to Dr. T. Wilson-Smith for allowing me to report those cases which were in his wards, to Dr. Philip Jones for his account of the fatal illness of the second case and for obtaining permission for the post-mortem examination, and to him and to Drs. A. J. B. Leckie and Verner Wiley for their assistance at the examination, and, finally, to Dr. R. A. Bayliss for his excellent micro-photograph.

REFERENCES.

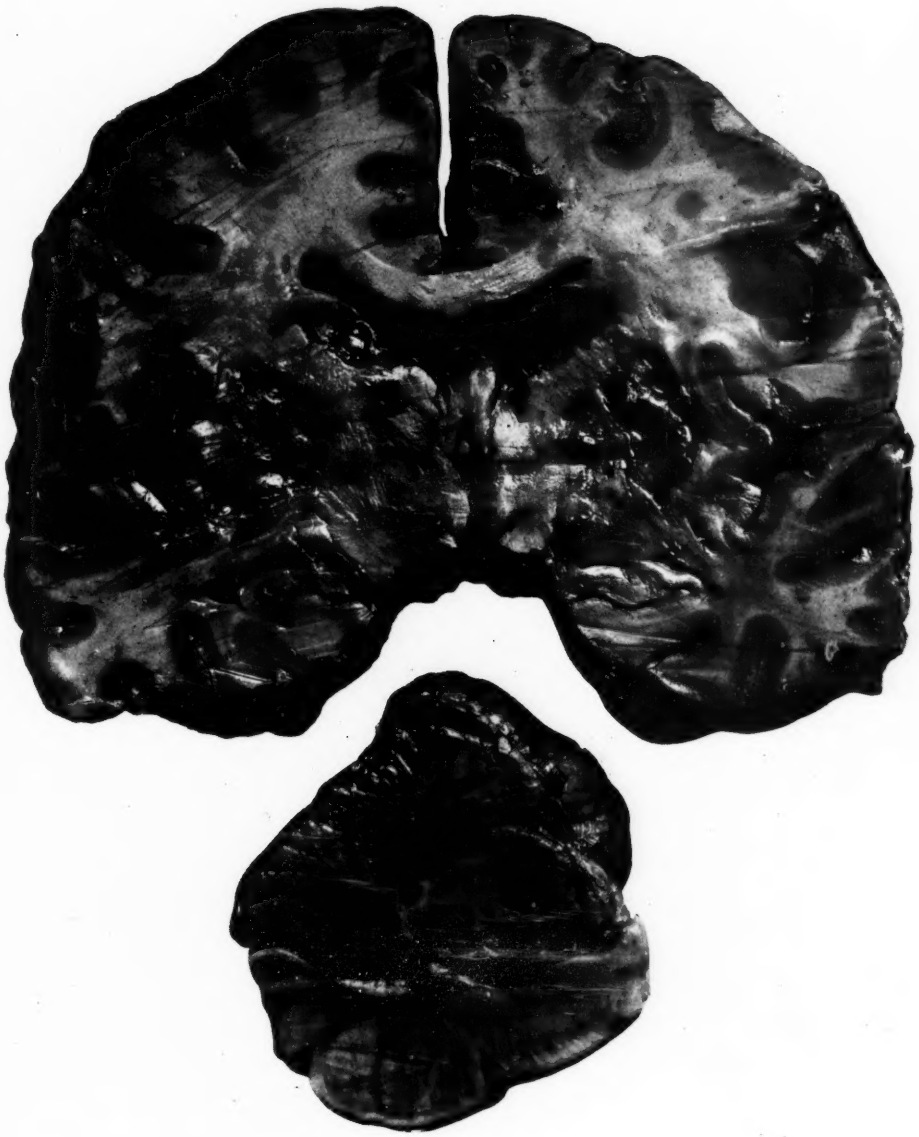
Alling, *Archiv. of Ophthalmology*, New York, 1909, xxxviii. 591.
Andrew, *Path. Soc. Trans.*, Lond., 1870, xxi. 4.
Barker, *Glasgow Med. Journ.*, iii. 439.
Bennett, *Med. Times and Gazette*, Lond., 1862, i. 80.
Birkett, *Guy's Hospital Reports*, Lond., 1860, 3rd ser., vi. 469.
Black, *Journ. Ment. Science*, Lond., 1903, xlix. 110.
Bristow, *Lancet*, Lond., 1866, i. 79.
Brittan, *Brit. Med. Journ.*, 1859, 272; and *Lancet*, Lond., 1881, i. 639.
Brunniche, *Med. Times and Gazette*, Lond., 1853, ii. 19.
Bruns, *Neurol. Centralbl.*, Leipz., 1902, xxi. 565.
Burgiss, *Brit. Med. Journ.*, 1862, i. 627.
Burton, *Med. Times and Gazette*, Lond., 1862, i. 158.
Canton, *Lancet*, Lond., 1848, ii. 91.
Carr, *Brit. Med. Journ.*, 1890, ii. 791.
Chotzen, *Neurol. Centralbl.*, Leipz., 1909, xxviii. 680.
Cobbold, T. S., *Entozoa*, 1864, 224; and [Quain's *Dict. of Med.*, 1885, 323; and *Entozoa*, Supplement, 1869.
Dagleish, *Lancet*, Lond., 1831–2, ii. 168.
Delore, *Compt. rend. Soc. de Biol.*, Paris, 1863–4, 3rd ser., v. 62.
De Renzi, *La Semaine méd.*, Paris, 1908, xxviii. 382.
Dianoux, *ibid.*, Paris, 1909, xxix. 595.
Dupuytren, *Lancet*, Lond., 1832–3, i. 739.
Fletcher, *Assoc. Med. Journ.*, 1855, iii. 161.
Flint, *Lancet*, Lond., 1881, i. 574.
Fredault, *ibid.*, 1847, i. 592.
Gellerstedt, *Dublin Quarterly Journ. Med. Sci.*, 1854, xvii. 253.
Griesinger, *Archiv d. Heilkunde*, Leipz., 1862, iii. 207; and *Brit. and Foreign Med.-Chir. Rev.*, Lond., 1863, xxxi. 250.
Gulliver, *Med.-Chir. Trans.*, Lond., 1841, xxiv. 1.
Gulliver, *Path. Soc. Trans.*, 1886, xxxvii. 60.
Harley, J., *Lancet*, Lond., 1867, i. 612.

Hedinger, *Month. Journ. Med. Science*, 1841, i. 749.
Heller, *Von Ziemssen's Encyclopaedia*, 1875, iii. 595 ; and *Lancet*, Lond., 1847.
Henneberg, *Charité-Annalen*, Berlin, 1906, xxx. 202 ; and *Monatsschrift f. Psych. und Neurol.*, 1906, xx. 28.
Hutchinson, *Path. Soc. Trans.*, Lond., 1857, viii. 408.
Huxley, *Brit. Med. Journ.*, 1868, i. 281.
Jones, *Path. Soc. Trans.*, Lond., 1863, xiv. 279.
Kirby, J., *Lancet*, Lond., 1837–8, ii. 590.
Knox, *ibid.*, 395.
Kuchenmeister, 'On animal and vegetable parasites of the human body,' *Syd. Soc.*, Lond., 1857.
Laignel-Lavastine und Halbron, *Bull. de la Soc. Anat. de Paris*, 1904, 6th ser., vi. 463.
Leuckart, R., *The Parasites of Man*, Edinb., Engl. transl., 1886.
McKendrick, *Lancet*, Lond., 1865, ii. 286.
Manson and Shipley, *Allbutt and Rolleston's Syst. of Med.*, Lond., 1907, ii. Part II.
Morrah, *Med.-Chir. Trans.*, Lond., 1811, ii. 260.
Mosler und Peiper, *Thierische Parasiten*, 2te Aufl., 1904, 121.
Moussu, *Compt. rend. Soc. de Biol.*, Paris, 1910, lxviii. 720.
Osterwald, *Neurol. Centralbl.*, Leipz., 1906, xxv. 265.
Ottley, *Lancet*, Lond., 1843–4, i. 368; and *Med.-Chir. Trans.*, Lond., 1844, xxvii. 12.
Perrin, *Brit. Journ. Dermatol.*, Lond., 1892, iv. 334.
Pye-Smith, *ibid.*, 366.
Riche et Carrié, *Arch. de Neurol.*, Paris, 1909, ii. 209.
Shillitoe, *Path. Soc. Trans.*, Lond., 1863, xiv. 170.
Siebold, von, 'On Tape and Cystic Worms,' *Syd. Soc.*, Lond., 1857.
Stephens, *Ann. Trop. Med. and Parasitol.*, Liverpool, 1908–9, ii. 391.
Stern, *Zeitschr. f. klin. Med.*, Berlin, 1907, lxi. 64.
Stewart, J., *Lancet*, Lond., 1848, ii. 103.
Sullivan, *Journ. Ment. Sci.*, Lond., 1903, xlix. 115.
Tanner, J., *Prov. Med. Journ.*, 1843, v. 150.
Thomson, T., *Trans. Lond. Med. Soc.*, 1837–8, ii.
Thouvenet, *La Semaine médicale*, Paris, 1911, 271.
Virchow, *Brit. and For. Med. Chir. Rev.*, 1858, xxi. 521.
Wilson, E., *Lancet*, Lond., 1848, ii. 143.
Wollenberg, *Archiv für Psychiatrie*, Berlin, xl. 98.
Ziegler, *Pathological Anatomy*, New York, 1896–7.

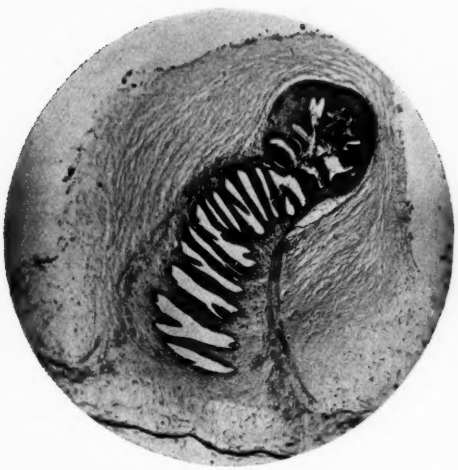
DESCRIPTION OF PLATES.

PLATE 26. Microphotograph of section through the scolex inverted in the cyst removed from Case 1. The rostellum, four hooklets, and two suckers are plainly visible. Stained with haematoxylin.

PLATE 27. Photograph of coronal section through cerebrum of Case 2, showing numerous cysticerci, most of which are in the grey matter of the cortex. The lower figure is a photograph of a sagittal section through the cerebellum and pons and shows a cyst with its contained scolex in the fourth ventricle : the cyst has collapsed as the result of accidental puncture.









ON PNEUMOTHORAX TREATMENT OF TUBERCULOSIS OF THE LUNGS

By O. AMREIN and F. LICHTENHAHN

With Plates 28–31

I

For some years past, several authors have noticed an astonishing alteration and improvement, with disappearance of the fever, diminution of the cough and expectoration, in bad progressive cases of tuberculosis with high pyrexia, in consequence of a pneumothorax, which had spontaneously appeared.

Such authors were Spaeth, Bäumler, Gaillard (who called the developing of pleural effusions compressing the damaged lung, 'Pleurésies providentielles'), and Lucius Spengler, who was one of the first to describe a healing of the affected lung by means of a spontaneous pneumothorax or pleural exudation. Adams had, in 1887, already discussed the question whether it would not be wise to produce an artificial pneumothorax, as he had seen cases in which profuse and dangerous haemorrhages had, in consequence of a spontaneous pneumothorax, been arrested. Forlanini, however, tried the experiment. In 1894 he gave an account of a number of cases he had successfully treated with an artificial pneumothorax. He may, therefore, be called the father of the pneumothorax treatment. He gave the following instructions to produce an artificial pneumothorax:

One of the finest injection needles should be inserted very carefully and very slowly, especially at the first puncture, through an intercostal space, penetrating the skin and muscles, until the intrapleural cavity is reached. The needle is kept in communication with the nitrogen, which enters through it into the intrapleural space (*Deutsche med. Wochenschr.*, 1906, 1401). This method may be called *the method of puncture*, and does not need any narcotics. It was adopted later on by many surgeons, as Lexer and Adolf Schmidt, who advised the use of a *blunt* needle, to avoid a penetration of the pleura pulmonalis. Murphy advised a small preparatory cut to be carefully made through the muscles to the pleura costalis, and only when, in consequence of this, the pleura costalis is lying visible and free, to penetrate it with a blunt needle. He was in the habit of using nitrogen, and in 1908 gave an account of five cases, which were all successful, and without any serious influence on the circulation or the breathing. But he strongly insisted on not producing too high a pressure inside

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the thorax, so as to avoid a displacement of the mediastinum. Schell was the first to apply pneumothorax in a case of abundant haemorrhage.

Murphy's method of incising was then adopted by Brauer, and it is to him we owe the fact that the artificial pneumothorax can be produced without any danger. Murphy-Brauer's method is the one mostly employed now in Germany and Switzerland. The little operation can be made almost painless by local anaesthetics. Together with Brauer, Lucius Spengler (Davos) gave an account of his experiences and observations with the new treatment. Up to now this is the richest and largest material which has been published about artificial pneumothorax, with a quantity of technical details, and with quite a large number of astonishing results.

Von Muralt (Davos) and Saugmann (Veljefjord), as well as others, have also written valuable papers on this subject. Other authors have described the *physiological influence* of the pneumothorax upon the blood pressure and the circulation, viz. Lichtheim, Rosenbach, Tigerstedt, Knoll, Liven, Hrátek, Sackur and Aron, and it is most interesting to learn how extraordinarily well the heart and large blood-vessels are able to compensate for all the alterations produced through the collapse of the lung and displacement of the heart and of the mediastinum, or the torsion of the large vessels. It has been proved that at first the blood pressure is increased, but after some time becomes again normal. A bad sign is a continual diminution of the arterial blood pressure. Sauerbruch was able to show, by interesting experiments, that the cause of the dyspnoea which often soon appears after pneumothorax is not the elimination of the breathing function of the collapsed lung, as one would be inclined to think, but is due to the collapse itself. As the tonicity of the lung is diminished, more blood is circulating through the collapsed lung than through the other one, and the non-collapsed lung is receiving too little blood, and is not able to receive enough oxygen to prevent dyspnoea. After some time nature corrects itself. Cloetta found that the collapsed lung is better filled up with blood than a lung in inspiration.

Finally, we may refer to a recent admirable review of the whole subject by E. Rist (this Journal, 1912–13, vi. 259).

II

We have had the opportunity of making observations together on several cases of *therapeutical pneumothorax* during the last two years at Arosa, and we think it will be useful to give an account of our experiences, both favourable and unfavourable, as this new treatment, combined with the climatic treatment in our altitudes, is able to bring amelioration in some cases having a serious outlook.

As to our *technical procedure*, we have hitherto preferred the *cutting method* by Murphy-Brauer, because it seems to us to be without doubt the best: we found it of course unnecessary in the one case (No. VI) where pleural

effusion had appeared, and where we could introduce the nitrogen through the same needle by which we had taken out the exudation. If the general condition of the patient should render the cutting method inadvisable, we would not hesitate to produce the pneumothorax from the beginning by Forlanini's method of puncture. We are in the habit of performing the little operation in the following manner: After having carefully chosen, by physical examination, and before the X-ray screen once immediately before the operation, the place which would be most likely to be free of adhesions, and after careful disinfection of the skin, we apply a cocaine lotion (Schleich's lotion) to make the skin and the muscles anaesthetic. Generally we cut in directly above an intercostal space between the linea axillaris anterior and posterior. On patients with well-developed fat tissue the length of the cut is nearly 3 inches (8 cm.), to enable a good orientation in the deeper parts; on thin patients $2\frac{1}{2}$ inches (5 cm.) suffice. Bleeding is stopped in the usual way, and causes no difficulty. After having reached the intercostal muscles, it is advisable to proceed slowly, and with *blunt* instruments. It happened once with a patient with very thin muscles that we penetrated the pleura, and air entered, with, however, no bad consequences, except that a large emphysema of the skin ensued, as the nitrogen could find its way out again through the cleft in spite of careful sewing. It is not always possible to make the pleura visible, especially on fat patients, because the cocaine injected may make the tissues swell. Artificial light (e.g. with electric light for endoscopy) may be of assistance. If the small spot of pleura is visible, it shows as a grey bright and transparent membrane, through which the marbled surface of the moving lung can be seen.

Next, we pass through the pleura a blunt needle (Salomon's cannula). A distinct whizzing proves that air is entering, and we know that we have reached a free intrapleural space. Through the cannula a long catheter (as for urethral examination) is passed, and enables us to examine whether or not pleural adhesions exist. With clippers we fix the needle (or we put some tight stitches through the intercostal muscles around the needle), and the needle is attached to the pipe of the manometer. Generally distinct respiratory movements can be seen on the manometer. Nearly always we find on inspiration a negative pressure of 6–8 cm. water; on expiration −3–4 cm. water. The nitrogen (which we keep preferably at a pressure of ± 0) can now enter, and is aspired in consequence of the negative pressure of the intrapleural space up to the point where the pressure in the nitrogen bottle and that of the intrapleural space have become equal. When the pressure is increasing quickly (generally after 100 c.c. nitrogen up to +5–6 cm.) we may infer that adhesions are present in the neighbourhood of the needle, and in this case it will not be possible to produce a large pneumothorax. As to the amount of nitrogen given the first time, it must naturally depend upon the size of the free intrapleural space, upon the pathological and anatomical condition of the lung, upon dilatability of the mediastinum, and last, but not least, upon the subjective condition of the patient. Presently the development of dyspnoea will prevent our going on.

Where there were no adhesions, or scarcely any, we were able on several occasions to give up to 1,000 c.c. nitrogen without any particular discomfort from the commencement. After having noticed the pressure at the beginning and at the end, we take out the needle and close the wound as carefully as possible with tight stitches of the muscles and other tissues, and then apply a compressing bandage (leucoplast).

When there is no free intrapleural space, the needle very soon meets with a hard resistance, caused by adhesions, but it is possible to enter with the needle into clefts between these adhesions. It is just in these cases that the elastic catheter probe and also the manometer, which will not then show good movements, will tell us that we have not reached the intrapleural space. In about ten cases we found such obliterated intrapleural spaces, and nothing could be done but close the wound and try another place. In one such case there were apparently no thick adhesions, and without feeling any resistance we entered with the needle into the bronchial system, which we realized only by seeing no increase of pressure after having given a quantity of nitrogen. We were afraid that a pulmonary fistula would develop, but it did not happen. This case, however, clearly indicated to us how little pressure, even with a blunt needle, must be used.

All our patients bore the trifling operation well. When it is finished we take the patient again before the X-ray screen, and if the production of a pneumothorax has been successful, we can distinctly see the large bright area of the pneumothorax, and the collapsed lung, which is generally pressed against the vertebral column, and shows itself as a lengthy shadow, distinctly demarcated. We generally keep our patients one or two days at the doctor's house, in order to give the second injection with nitrogen (only by puncture) without any transport. The after-injections are given as necessity may indicate. As a rule the first one is given after the first or second following day, so as to keep the pressure on +0.

Before commencing the first operation and the other punctures it is necessary to give the patient some codein or heroin, to prevent much coughing during the filling. After a few days the patient is able to return home. The succeeding punctures are given as of necessity: during the first months the injections have to be repeated more frequently, as the nitrogen is absorbed quickly by the pleura. A further puncture, therefore, will be necessary every ten to fourteen days. When physical examination and the X-ray screen indicate that the lung is remaining compressed, the intervals become longer, and towards the end of the first year a refilling every six to eight weeks will suffice. The *duration* of the whole treatment will depend upon the special case. As generally only very advanced cases are treated with artificial pneumothorax, the duration of maintaining the pneumothorax will usually be about one year, for after that time we may expect a definite fibrous shrinking of the affected lung; but in cases of large cavities a durable result cannot be expected within two years, especially as in such cases a total compression cannot often take place

from the beginning, in consequence of strong adhesions of the wall of the cavity.

When there are no adhesions the operation of artificial pneumothorax is a very simple one. The first principle must *always be not to do anything without the control of the manometer.* Without doing so all the manipulations are only a tapping in the dark. Also, one must never forget the danger of an embolism of air, and must try to avoid it. This can be avoided if we do not allow the entrance of nitrogen without distinct evolutions of the manometer. Also, we must not forget to push the probe of the catheter through the needle, to be sure the needle is not blocked. Personally we attach much value to the mandarine (urethral probe), which should exceed the needle in length by about 1 cm. ($\frac{1}{3}$ inch) with its blunt not pointed end. It shows us whether the end of the needle really does glide in to a free intrapleural space, or whether we meet with adhesions, and if, with deep breathing, the mandarine does move back, we know that we have touched the surface of the lung itself. Many authors have noted the danger of an *embolism of gas* in the blood-vessels as a consequence of admitting nitrogen, but, with a knowledge of its disastrous effects, we should take care that it should not happen.

The practitioner desirous of employing the method himself will find a quantity of technical details in Forlanini's lengthy paper (*Ergebnisse der inneren Medizin und Kinderheilkunde,* 1912, ix. 621) and in that by Muralt ('Manometrische Beobachtungen,' &c., *Beiträge zur Klinik der Tuberkulose,* xviii).

As to the apparatus and instruments, we use those recommended by Brauer and Spengler, which can be obtained from Holzhauer at Marburg. A very useful manometer is the one introduced by Cloetta. The simpler the apparatus, the better and easier it can be managed.

The X-ray apparatus is of the greatest importance. Our habit is to take an X-ray photo before we decide whether we shall try an artificial pneumothorax or not, principally in order to know whether the other lung is sound enough. Moreover, the X-ray screen is of great value in comparing existing conditions between the different punctures. It is certainly possible, in urgent cases, to produce an artificial pneumothorax without the assistance of the X-rays, and we have had to do it ourselves in some cases, but it ought to be a rule not to operate without the control of the X-rays, or in a house where there is not a fully equipped X-ray installation.

III

We now append a brief account of our personal experiences in cases treated by artificial pneumothorax, and a *résumé* of our successes, failures, and conclusions will be faithfully noted.

Case I. Mr. W., merchant, aged 45 years. Four sisters and brothers have died of tuberculosis of the lungs. One sister is still alive, but also consumptive. Sixteen years ago the patient suffered from acute nephritis. In the autumn of

1908 he fell ill with cough, fever, and abundant expectoration, nevertheless continuing his work, being a busy man. Dyspnoea soon appeared, accompanied by fever and weakness, loss of appetite and weight, and frequent attacks of high fever. Tubercle bacilli were found at the commencement of the illness. It was only in August, 1910, that he came to Arosa, and, as one would expect from his neglect of his illness, he was a terrible picture of progressive tuberculosis of the lungs. The *right* lung was completely infiltrated. Intense dullness on percussion was found over the whole upper lobe, with tympanitic sound and the symptoms of cavities (amphoric breathing, and very many consonant râles). The right middle and lower lobes showed bronchial vesicular breathing, with many râles and crepitations, less dense, however, than at the upper lobe.

In the *left* lung there was slight apical dullness down to the second rib and the spine of the scapula: very few dry crepitations; the rest of the lung showed good vesicular breathing with an absence of crepitations. In short, we found a total infiltration of the entire right lung with a large cavity in the upper lobe, and infiltration of the two other lobes, and a slight affection of the left apex. Whether the few crepitations at the left apex were transmitted to the ear from the other side is difficult to decide. The patient remained in bed for four months, without any distinct amelioration. The temperature went down a little, but invariably rose up to 37·5° C. and 38° C. The physical condition did not change much, with the exception of a diminishing of the râles at the right lower lobe. His expectoration was enormous, and contained numerous bacilli and elastic fibres. As the prognosis was unfavourable, we proposed an artificial pneumothorax, and the operation was performed on December 21, 1910, in the fifth intracostal space at the right linea axillaris anterior. After having penetrated the pleura with the blunt needle, air entered with a noise, and the manometer showed distinct respiratory undulations and a high negative pressure. We put in 500 c.c. nitrogen. The pressure went up to + 4 cm. Immediately after the operation, the X-ray screen showed us already a compression of the middle and lower lobes towards the vertebral column. But the large cavity at the upper lobe was not compressed on account of strong adhesions (Fig. 1). The patient evinced no discomfort except slight increased dyspnoea. Two days afterwards (December 23) another 400 c.c. nitrogen were admitted. The pressure went up to +5 cm. In the neighbourhood of the incision slight emphysema was apparent, but disappeared in the course of eight or ten days. Afterwards we admitted nitrogen (by puncture) every eight to ten days, and, later on, every three, four, or six weeks, and during all this time the pressure was kept to a height of +1 cm. to +4 cm. The quantity of nitrogen admitted again was 600 c.c. After each time of refilling we were able to see, before the X-ray screen, the adhesions which fixed the lung to the diaphragm (Fig. 1) become gradually looser. The cavity at the upper lobe was partly collapsing. But a complete collapse did not take place on account of too strong fixation by adhesions.

The *clinical state* changed wonderfully from the very moment of the production of the pneumothorax. The very day after the operation the patient

was free from fever, and during the whole following year the temperature did not go higher than 37·1° C. The pulse became better and stronger, and the patient himself said he felt better in every way. The expectoration diminished in quantity, a certain amount, however, persisting, on account of the incompletely compressed cavity. The patient put on weight, and was able to walk a little, but always with some evidence of dyspnoea.

Nine months after the operation oedema in the feet and albuminuria (12 per cent.) appeared, with distinct signs of amyloid degeneration of the kidneys, and he died with general dropsy on December 24, 1911, just a year after the production of the pneumothorax.

The autopsy showed: *the right lung*, the size of a large fist, lying closely along the vertebral column, except the upper lobe, which was strongly adherent to the pleura costalis. In the centre of the apex a cavity was situated in the midst of thick fibrous tissue, as large as a walnut. All the rest of the lung showed hard fibrous tissue with many very small nodules of grey yellow colour as large as a pea: no softening process was to be found. *The left lung* was very voluminous. At the apex there was a small tuberculous knot of the size of a small hazel nut: the upper and lower lobes showed small fibrous tuberculous foci without any softening process. The intrathoracic glands were slightly enlarged with anthracosis.

Conclusion. Mainly monolateral tuberculosis of the lungs. Prognosis unfavourable. In consequence of the artificial pneumothorax a further development of the disease was averted, and the toxic influence of the large infiltration of the right middle and lower lobe was eliminated, as shown by the disappearance of the fever. A complete cure was impossible on account of the large cavity, but this had become smaller by a half during the year of the duration of the pneumothorax. It was, however, impossible to eliminate the influence of the intoxication of the whole organism, after some years of illness, and entirely to check the secretion of the cavity. The fatal issue was entirely due to the amyloid degeneration of the kidneys, which had been diseased for sixteen years. The condition of the compressed lung, as shown at the autopsy, was absolutely satisfactory, from the point of view of the success of an artificial pneumothorax.

Case II. R., aged 26 years, *chef de cuisine.* Family history good. Polyarthritis in his youth. In 1904 he showed symptoms of a breakdown by haemoptysis, and, notwithstanding frequent repetitions, he still stuck to his work in 1905, 1906, 1907, and 1908. In 1909, however, he came to Arosa, very enfeebled, and showing over the entire left lung slight dullness on percussion, vesicular breathing on inspiration, rough expiration, with many crepitations and râles. At the base of the right lower lobe there was slight dullness with very few crepitations, which, after climatic treatment for a month or two, disappeared. The expectoration was relatively small in quantity. The patient went to work again as cook until January, 1911, and showed signs of distinct improvement; during this month, however, there was increased irritation of the left lung, and, though he was confined to bed, it was followed by profuse

haemorrhage and there was a continuance of haemoptysis till the middle of February. Although there was an absence of fever, and the patient felt quite well, he was compelled to remain in bed. The persistent haemoptysis, as well as the apparent increase of disease in the left lung, indicated the advisability of trying an artificial pneumothorax.

The *operation* was performed on the 27th in the fifth intracostal space on the left side at the linea axillaris anterior. The blunt needle without difficulty entered the intrapleural space. The manometer showed good undulations from −2 to −4 cm. water. Admission of 800 c.c. nitrogen slowly; the pressure, therefore, shows an amount of +2½ cm. (water). Before the X-ray screen we saw a large pneumothorax, the lung compressed towards the vertebral column and very well separated from the diaphragm. At the apex very few thin adhesions; displacement of the heart to the right side. The patient felt weak and fainting, but quickly recovered. Pulse good, scarcely any dyspnoea, and very little emphysema under the skin. Up to May 23, 1912 (1½ years), nineteen punctures with nitrogen were given, generally 1,000 c.c.: the pressure meanwhile remaining +1 to +4 cm.

The *clinical effect* was that desired. The haemoptysis, which persisted for six weeks, entirely ceased and did not recur. In the course of a few weeks the patient began to work again, and was able to take up the occupation of an hotel-keeper in Arosa. Cough and expectoration have entirely disappeared, and the temperature remains quite normal.

After feeling perfectly well and fit the patient did not deem it necessary, after the last puncture in May, 1912, to remain under medical supervision, and, as his wife says, had not been at all careful, discarding rest for some hours on his chair every day, as he was told to do, &c. In November he returned to medical treatment with high fever, considerable expectoration, and a pleural effusion at the left lower lobe, which enabled us to produce a pneumothorax again, which had entirely disappeared. But the state of the entire left lung was much worse again, and it is a pity that such a perfect success was paralysed through the carelessness of the patient.

Conclusion. Monolateral tuberculosis of the whole left lung, with tendency to haemoptysis, which indicated the necessity of an artificial pneumothorax. In this case the haemoptysis was entirely checked. There was a general amelioration and capacity to resume work. Seven months afterwards, when all the nitrogen was absorbed, a relapse (entirely due to his own carelessness) occurs, rendering the prognosis extremely doubtful. In future, with similar cases, we shall go on with the punctures for a long time, if only to keep such a patient under medical control. The success in this particular instance can be claimed as definite, and the haemoptysis was completely checked.

Case III. Miss O., aged 22 years. Family healthy. As a child suffered from scrofula; later on chlorotic. Four years previously she was laid up with pleurisy at the left side, with fever up to 40° C., for three months. Since then she had resided at different health resorts. Haemoptysis frequently occurred, and

often long periods of high fever, with constantly increasing purulent expectoration. For the last two years she had also suffered from laryngeal trouble. She arrived at Arosa on October 10, 1911, in the following condition: the whole *left* side showed tuberculous infiltration, tympanitic sound at apex with symptoms of cavity, and broncho-amphoric respiration, with many râles and metallic sounds. At the left lower lobe dullness on percussion (adhesions), but sharp broncho-vesicular inspiration and bronchial expiration, many consonant râles. Over the *right* lung sharp inspiration transferred râles from left side. The patient had no fever, but was dyspnoeic, and had abundant expectoration with B. tuberculosis. In the larynx the vocal cords were swollen and ulcerated. After three months' residence in Arosa no improvement was perceptible, and the patient herself expressed a wish to try the pneumothorax. It was doubtful from the beginning whether a pneumothorax could be produced, as the whole lower lobe showed thick adhesions.

The *operation* was performed on January 3, 1912, as high as possible: third intercostal space, linea axillaris media. After penetrating the pleura costalis, the manometer showed good oscillations (−3 cm. water). After an introduction of 100 c.c. nitrogen, the pressure went up at once to +5 cm. water; a further 200 c.c. nitrogen were introduced under a high pressure, and the manometer registered +15 cm. water. Before the X-ray screen we saw that the cavity at the upper lobe was compressed to half its size, the pneumothorax being only a partial one from the fourth rib upwards. For the next $2\frac{1}{2}$ months we attempted, by frequent punctures and with a high pressure, to obtain a large pneumothorax and a better compression of the lung, but without success, the adhesions at the lower lobe being too strong. The patient being very sensitive and complaining of severe pain after the punctures, the treatment was discontinued in the middle of March, 1912. Immediately after the operation the amount of expectoration decreased to one-third, in consequence of the compression at the apical cavity, and even after the cessation of the treatment the expectoration did not again increase. The patient lived with great care and felt very well. We are justified in saying that there was increasing retraction of the whole left side, and the outlook therefore hopeful.

Conclusion. Advanced monolateral phthisis with large apical cavity. The operation produced a compression, and the expectoration was greatly and definitely reduced. Contrary to our expectations, it was possible to produce a partial pneumothorax in a case which *a priori* did not seem to be a favourable one for this form of treatment.

Case IV. Mrs. D., aged 23 years. Family history good. Cough, expectoration, high fever with loss of strength supervened in February, 1911, after her confinement. In the following October she came to Arosa, and showed on arrival tuberculous infiltration of the entire left lung, and very many consonant râles, especially at the left lower lobe. She was kept in bed for three months; temperature every evening rising to 38° C.; much cough and expectoration; visibly losing ground. As the right lung showed no sign of disease, we suggested the

pneumothorax operation, which was performed on January 22, 1912, in the fourth intercostal space, on the linea axillaris sinistra. The manometer showed good oscillations (−4 cm. water), and after the introduction of 1,200 c.c. nitrogen we obtained a pressure of +5 cm. water. Before the X-ray screen we found a complete pneumothorax, the entire left lung being compressed and lying along the vertebral column. Only one slight adhesion with the diaphragm was visible. With six punctures the pneumothorax was sustained until the middle of April, 1912, 700 c.c. nitrogen having been introduced each time, on an average, with a pressure of +2 cm. water. A complete and continued compression of the lung was possible.

The *clinical success* was very good. From the day of the operation fever entirely disappeared, and after a few days cough and expectoration rapidly diminished, and soon entirely disappeared. In ten days after the operation the patient was able to walk about, feeling stronger and better.

She left Arosa in the middle of April for her own home, where the punctures in order to admit nitrogen were continued at considerable intervals. Her doctor informs us that she keeps very well, without cough, expectoration, or fever.

Conclusion. In this case of advanced monolateral tuberculosis, evidencing activity and deterioration, the operation of pneumothorax produced a wonderful effect. In a short time all symptoms of deterioration and toxity were completely arrested.

Case V. Mrs. P., aged 34 years. One brother suffered from tuberculosis of the lungs. She fell ill in August, 1911, with cough, expectoration, and fever up to 40° C. She had been, however, in a debilitated condition for some years previously. She remained some months in a sanatorium at Davos, suffering from continual fever. At the end of January, 1912, she came to Arosa. The whole *right* lung showed dullness on percussion, with bronchial vesicular breathing, and very many large consonant râles and fine crepitations from the top down to the base of the right lung. Some pleural rubbing was to be heard at the base of the left lung. Three months later the patient was laid up with fever, the temperature rising to 38·1° C. On April 1 there was a diminution of fever, but it recurred with greater intensity after short intervals. Cough and expectoration at this time remained very troublesome, and there was no visible amelioration in her physical or general condition.

Pneumothorax *operation* performed on July 11, 1912, in fourth intercostal space, in the right anterior axillary line, without any difficulty and with good manometer oscillations. After the introduction of 1,000 c.c. nitrogen, the manometer showed a pressure of less than +1. Before the X-ray screen the whole upper lobe was seen to be totally compressed, while some adhesions hindered a complete compression of the middle and lower lobes. After ten punctures, with, on an average, 1,000 c.c. nitrogen and a pressure of +4 cm. water, the pneumothorax continued to increase. Some adhesions disappeared, and the compression of the upper lobe became complete. From the day of the operation the patient's

temperature was absolutely normal. Five months after the operation she felt strong and well, being able to take long walks every day. Cough and expectoration nearly disappeared. Lately, this patient has been careless and doing too much in her household, and, consequently, a further increase of cough and expectoration occurred, but these were checked by another injection. With more frequent punctures we shall maintain a total compression.

Conclusion. Advanced monolateral tuberculosis of the right lung, with pyrexia. After operation, disappearance of fever, decrease of cough and expectoration. A durable result is probable, although the patient is not sufficiently careful, thereby undergoing considerable risk.

Case VI. Miss L., aged 22 years. Her mother suffered ten years ago at Davos with pulmonary tuberculosis. The patient became ill three years ago with cough, expectoration, and fever. After fifteen months at an English sanatorium, and a further stay at an altitude of 3,200 feet over the Rhone valley for ten months, she evinced no signs of permanent improvement. She came to Arosa on September 16, 1912, appearing to be an absolutely hopeless case, with cachexia, dyspnoea, palpitations of the heart, night sweats, anorexia, and abundant thick purulent expectoration. The entire *left* lung showed dullness on percussion, with tympanitic sounds over the upper lobe and other evidences of cavity. Sharp broncho-amphoric breathing, metallic and consonant râles, with a whizzing sound over the whole upper lobe. Over the lower lobe there were bronchial vesicular breathing, many small crepitations, and consonant râles, with some pleural rubbing at the base. The action of the heart was very weak; the pulse quick, small, and irregular. The expectoration contained a number of tubercle bacilli and elastic fibres.

For eight weeks the patient was laid up in bed with hectic fever and increasing cough, which became at times so violent that eating was almost invariably followed by vomiting. She was visibly losing ground; the heart became weaker and had to be stimulated by camphor and digalen. We had, from the very commencement of our treatment, considered the advisability of a pneumothorax, but her weakness contra-indicated it, as well as the recurrence of dry pleurisies. In the early part of November fever still increased and a fresh pleural irritation supervened. On the 8th a more intense dullness on the left side was perceptible. A puncture showed the presence of a clear serous fluid, and with this condition it was possible to enter into the intrapleural space, without any operation and with great facility, even without moving the patient from her bed in the hotel. On November 11 we entered into the intrapleural space with a Saugmann needle and removed about 30 c.c. of fluid by aspiration. Immediately after that the manometer showed a negative pressure of 8 cm. water and good respiratory oscillations. With the utmost carefulness we introduced nitrogen, always controlling the pressure after each 200 c.c. The existing dyspnoea was not greatly increased, and we were able to introduce 1,000 c.c. nitrogen, obtaining a pressure of +2 cm. water.

As was to be expected, the patient exhibited symptoms of shock and

increased dyspnoea, and it was necessary to give her inhalations of oxygen. But, after four to five hours, the dyspnoea diminished and she felt relieved. After three other punctures (it was possible twelve days after the initial one to make a puncture in the physician's house, with control of the X-ray screen), introducing on each occasion 500 c.c. nitrogen, we were able to maintain a pressure of +1 to +4 cm. water. The X-ray screen showed the left lung compressed to more than half its size. The punctures were continued every two or three weeks; on each occasion there was some dyspnoea for a few hours, with acceleration of the pulse; these symptoms were, however, quite natural, considering the prolonged cachectic condition before the operation, the weak action of the heart, and afterwards its displacement.

The *effect* of the compression of the left lung was quite miraculous. By the evening of the first operation the fever, which had been for three years persisting, entirely disappeared; the pulse dropped from 140 to 92, its quality becoming fuller and stronger. The expectoration diminished to one-fifth of its volume, and sleep was obtained without the aid of narcotics. The appetite returned, and altogether the general amelioration was astonishing.

Naturally, the patient was still weak, but, two months after the production of the pneumothorax, she still continued afebrile, and there was no increase of expectoration.

Conclusion. Advanced tuberculosis of the entire left lung with a hopeless prognosis: high hectic fever for three years, abundant expectoration; a picture of general deterioration and daily loss of ground. But, after the compression of the lung, there was instant cessation of the fever, with decrease of sputum to one-fifth of its quantity! Five months only have lapsed since the production of the pneumothorax, and a very considerable time must pass before a definite healing takes place, but we are justified in hoping that this healing will be effected, if the organism, which for so long a time was weakened and intoxicated, has sufficient power of resistance to conquer the alteration of the circulation. In any case, this patient's life has been for the moment saved by the production of an artificial pneumothorax.[1]

The above cases, which we have described in detail, indicate how successful the pneumothorax treatment can be if individual subjects be carefully selected, and, moreover, how some patients, whose lives are despaired of, may be brought back to a healthy condition.

We shall now give a brief account of some further cases, where the production of an artificial pneumothorax was not so definitely successful—some more, some less—but we trust they may prove interesting.

Case VII. Mr. T., aged 28 years. Ill since 1907. Confined to bed since December, 1910, after a large haemoptysis, with advanced affection of the right lung. In the spring of 1911, an artificial pneumothorax was performed by Dr. von

[1] Seven months have now elapsed (June), and the patient has recovered in a miraculous way to a strong person who is able to walk without any difficulty, has increased in weight, shows constant normal temperature, and has become quite another person.

Muralt in Davos. There were so many adhesions at the top of the upper lobe that a partial one only was possible. A distinct amelioration has since resulted, with complete absence of expectoration. In the summer of 1912 he came to Arosa, where we punctured him on two occasions, with the view of maintaining the pneumothorax. In consequence of the numerous adhesions, the pressure increases even after the introduction of only some hundred c.c. nitrogen, but the patient feels strong and well, and the prognosis is good.

Case VIII. Miss L. For many years ill with advanced tuberculosis of the left lung, with a large cavity at the upper lobe. The right upper lobe shows infiltration. In 1911 an artificial pneumothorax was produced at Davos. The left apex only could be collapsed, resulting in reduction of sputum. During the winter of 1911–12 we here in Arosa maintained the small pneumothorax with frequent punctures, but we found it impossible to check the progress of the disease in the right lung, and the patient is losing ground.

We are of opinion that the production of an artificial pneumothorax was not successful because both lungs were affected, but as the patient centred all her hopes on the pneumothorax treatment, we did all in our power to maintain the small one produced at Davos.

Case IX. Mr. G., aged 27 years. Had been suffering from tuberculosis of the right apex for six years, of which he became cured at Arosa. In October, 1911, however, after a haemorrhage, high fever set in and the disease advanced, spreading over the right lung, and also to the left apex, with abundant sputum full of bacilli. He was then residing in his native town in the plains, and very shortly after the appearance of the above symptoms an artificial pneumothorax was produced with nearly 2,000 c.c. nitrogen! In spite of acute dyspnoea, a further 1,000 c.c. nitrogen were introduced in the course of a few days: the pressure went up to +16 cm. water. After the operation, during the first week, the temperature was good, but after each further puncture showed a rise, and, a reported by his local physician, crepitations began to be heard over the 'healthy' left lung. He arrived at Arosa at the end of December, 1911. Before the X-ray screen a large pneumothorax on the right side was visible. The patient was very dyspnoeic, but without fever. The left lung exhibited fine crepitations at the lower lobe, and vesicular bronchial breathing over the whole side. In January, 1912, nitrogen was introduced by a fresh puncture, only to a pressure of −1 cm., in consequence of the suspicious state of the left lung.

At the beginning of March, 1912, he fell suddenly ill with rigors and high fever. At the right side there was evidence of a rapidly developing exudation, which very soon extended up to the third rib. Over the left lower lobe a new infiltration, with bronchial breathing and numerous râles, set in. By aspiration we removed the exudation, as well as the remaining nitrogen present, from the right side. As a result the dyspnoea diminished, but high fever was persistent (38·2° C. daily), and shivering attacks with sickness recurred every 10–14 days. The fever went up as high as 40° C., and then slowly there was a defervescence. The râles increased on both sides, but more especially at the left side. The case

exhibited a typical picture of a consistently progressive tuberculous pneumonia; with loss of appetite, and the action of the heart becoming daily weaker, the outlook was, in a word, hopeless. His personal desire was to be transferred to a private hospital at Zürich, where he died in June, 1912. No autopsy was allowed.

There is no doubt that in this case the production of a pneumothorax did the greatest possible harm. The physician in charge who performed the operation did not watch, with sufficient care, the other apparently 'healthy' lung. Without the most careful observation, especially with regard to the other lung, an artificial pneumothorax is not permissible, except in cases of profuse haemorrhage with immediate danger to life. It is only after a recognition, resulting from the observation of several weeks, that the tuberculous process is unilateral, that we may be permitted to advise the production of an artificial pneumothorax.

Case X. Mr. T., aged 26 years. A resident at Arosa since May, 1909. Advanced tuberculosis of the entire right lung, with infiltration of the left apex. Having been laid up with fever for five weeks, the patient became apyretic. A general improvement was manifest during the following two years, but this was less marked in the condition of the right lung. In March, 1911, he suffered from a relapse, after an attack of influenza, but during the summer he recovered and his condition was satisfactory. In November, 1911, haemoptysis set in, continuing till December 1. The patient was visibly losing ground, and his condition was alarming. On December 25 an artificial pneumothorax was produced while he was in bed. On account of multiple adhesions a partial one only was possible. But the high pressure was efficacious in checking the haemorrhage. The presence of adhesions was a bar to increasing the pneumothorax by further punctures, and as the other lung showed progressive disease the treatment was discontinued. Later, smaller haemorrhages ensued, and after a further development of the disease, the patient died in May, 1912.

In this case an artificial pneumothorax was tried only as an *ultima ratio.* The anticipated effect (checking of the haemorrhage) was obtained, but no more could be expected.

Following on the above cases of artificial pneumothorax, we should like to mention one more, where its induction was not possible, but where the therapeutic procedure—the thoracoplastic—is intimately allied with the indications of the pneumothorax therapy. It is out of place here to enter into details of resection of ribs; we merely mention the following points.

The resection of ribs can undoubtedly produce a splendid result in cases where, on account of strong adhesions, the production of a pneumothorax is impossible. In such cases the complete compression of the affected lung is caused by the straightening (or diminution) of the intrathoracic space, by the cutting out of pieces of some ribs, instead of filling up this space with gas. It is universally recognized that the operation is not a trivial one, and that it should be attempted only by well-trained and experienced surgeons. The

physiological effect upon the diseased lung is the same as in cases treated with pneumothorax, and several surgeons (Friedrichs, Sauerbruch, &c.) have noted good results in cases where life was despaired of.

Case XI. Miss P., aged 34 years. Tuberculosis of the left apex for the past seventeen years. In 1898 fever and expectoration. In 1900 a fresh advancement of the disease. Consequently the patient came to Arosa and remained here till 1901. There was the evidence of tuberculous affection of the whole left lung, with cavities. She recovered in an astonishing manner, and returned to Zürich. In 1902 she came back to Arosa with fresh fever, following upon an operation (curetting of a laryngeal ulcer). She improved in health so satisfactorily that she was able to keep a *pension*. In the spring of 1908 a considerable pleural exudation of the left side was manifested, provoking high fever, and the exudation reabsorbed slowly. During the entire summer she was laid up in bed with fever, and the disease of the left side gradually became more intensive. For the two succeeding years the progress was intermittent: at one time, improvement; at another pyrexia, with attacks of bronchial catarrh, and abundant expectoration. In the summer of 1911 the patient was desirous of trying an artificial pneumothorax. But, on account of the strong adhesions, a successful result could scarcely be expected. The succeeding winter she was nearly always in bed, the fever constantly present. For several years previously there had been an infiltration of the right upper lobe, but it was stationary. In the spring of 1912 the patient, hoping against hope, expressed a desire to go to Zürich to try the effects of a thoracic operation. It was manifest that, in consequence of the infiltration of the right lung, the success of such an operation was very dubious, but there was the fact that the condition of that lung had been for some years stationary, and it appeared right to give the patient her last chance, her condition being wellnigh hopeless. The physicians in the Zürich hospital being of the same opinion, Professor Sauerbruch performed, on June 6, 1912, the operation of resection—excising three-inch pieces of the first seven ribs. Profound shock occurred after the operation, and the recovery was tedious, but with the result that the compression of the left side seemed complete, while the temperature dropped to normal. The expectoration diminished, and hopes were entertained that the patient was saved. Nineteen days, however, after the operation, high fever, rigors, and increasing dyspnoea set in. Over the right side bronchial breathing and numerous râles appeared, and after a further five days of painful dyspnoea the patient died from acute pneumonia on June 28, 1912.

The post-mortem showed a total compression of the whole left lung (Fig. 7), two large cavities being completely collapsed and absolutely dry (Fig. 8); all the other parts of this lung showed thick and hard cicatricial tissue, with no signs of fresh disease. The right lung showed induration at the upper lobe, and fresh peribronchial spots; in the lower lobe fresh pneumonia spots (aspiration pneumonia).

This case also shows us distinctly that for the production of an artificial

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pneumothorax, as well as for the resection of ribs, the indication must be made dependent upon the state of the other lung.

It is impossible to give a special and rigidly correct formula for this *indication*. An absolutely monolateral tuberculosis of the lungs does not often exist; but we must discriminate, from case to case, as experience teaches us. *General indications* may be classified as follows:

If there should be no urgent and vital indication, such as profuse haemoptysis or cachexia (and then the operation can only be advised as a forlorn hope), an observation of at least two months, but better still of three or four months or more, is necessary, with special attention to the other side, in order to pronounce definitely whether the 'healthy' lung exhibits no manifestation of activity. In special cases, medical experience will temper our decision. It is an obvious fact that it is a more simple matter to remedy an error after the production of a pneumothorax, by the removal of the nitrogen, than is possible after the thoracoplastic operation. We can, therefore, only advise this final and always serious operation after several attempts have shown the impracticability of an artificial pneumothorax.

Our personal experience with the pneumothorax treatment convinces us that many apparently hopeless cases of monolateral tuberculosis of the lungs *can* be arrested, and, further, *may* be healed; and even if perfectly satisfactory results are few and far between, the trial of the treatment is legitimate, provided that we always act on the highest medical principle: 'Nil nocere.'

Appendix (*June*, 1913).

Since we wrote the above (April, 1913) we have produced a pneumothorax in eleven other cases; in nearly all these cases, using the method of puncture from the beginning, our results were very good. It means much less strain for the patient, in comparison with the cutting method, and can be tried even on very weak patients. But we should like to say that it is very essential to have had a large amount of experience with the method of puncture both in producing and in maintaining an artificial pneumothorax. Without great care there is the dreaded danger of embolism. To avoid this danger we use oxygen for the first insufflation, after 100–200 c.c. have entered into the intrapleural space and the manometer shows distinct respiratory movements; nitrogen can be given afterwards by changing the communicating bottles.

Although this method of puncture is much more agreeable for the patient, we must not forget to observe very strictly the indications for the pneumothorax treatment, as, in consequence of the simpler apparatus, the decision for the little operation is taken too quickly and without forethought by the physician. We have to add further that we have seen some exudations, large and small, on patients where we had produced an artificial pneumothorax. They generally

are not of much consequence and the fluid is absorbed and the rise of temperature disappears. It is best not to remove the fluid unless there is a definite indication, but to maintain the pneumothorax. These effusions probably arise mostly from over-tension and rupture of pleural adhesions. (In one case we observed an infection with B. coli—we could not find out why—with development of an empyema which made the resection of a rib necessary. The patient was a weak woman who died after two months.)

DESCRIPTION OF FIGURES.

PLATE 28, FIG. 1 (Case I). Good compression of the right middle and lower lobe. The total compression of the cavity at the right apex is prevented by a strong adhesion. At the right-hand side emphysema in the subcutaneous tissue by nitrogen.

FIG. 2 (Case II). Large pneumothorax at the left side. The lower lobe pushed upwards. Strong adhesion at the apex. Dislocation of the heart to the right side.

PLATE 29, FIG. 3 (Case VI). Total tuberculosis of the left side, the right side absolutely intact.

FIG. 4 (Case VI). The same thorax immediately after the pneumothorax operation. Total compression of the left upper lobe, less compression of the lower lobe, heart not much dislocated to the right side.

PLATE 30, FIG. 5 (Case IX). Large pleural exudation of the pneumothorax side. The whole upper part of the left side filled up nitrogen. The compressed apex visible in a circular form underneath the insertion of the clavicle to the sternum.

FIG. 6. Photograph of a patient where a pneumothorax was made at another town in Nov., 1911. The right lung shows multiple infiltration; the induction of the pneumothorax was therefore risky. But the patient has done well up to now notwithstanding, has no fever and very little expectoration. A durable result, however, is doubtful.

PLATE 31, FIGS. 7 and 8. Photographs of the lungs removed after death (Case XI), showing the total compression of the left lung and the cavity in the left lung.

(Photographed at the Surgical Clinic, Zürich, published by kind permission of Prof. Sauerbruch.)

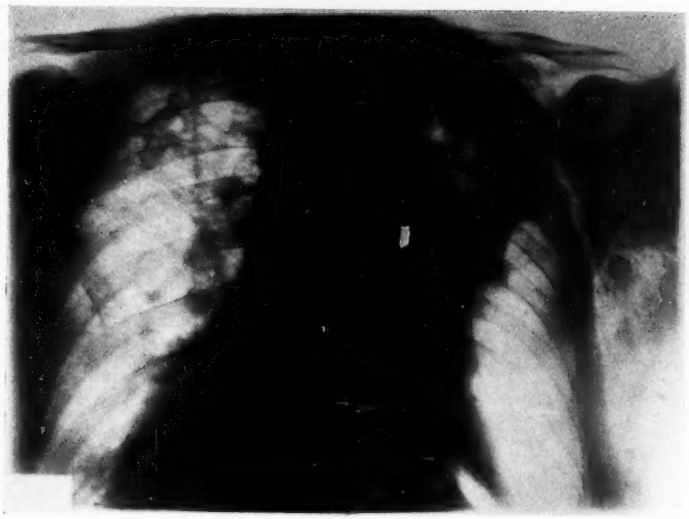


FIG. 1

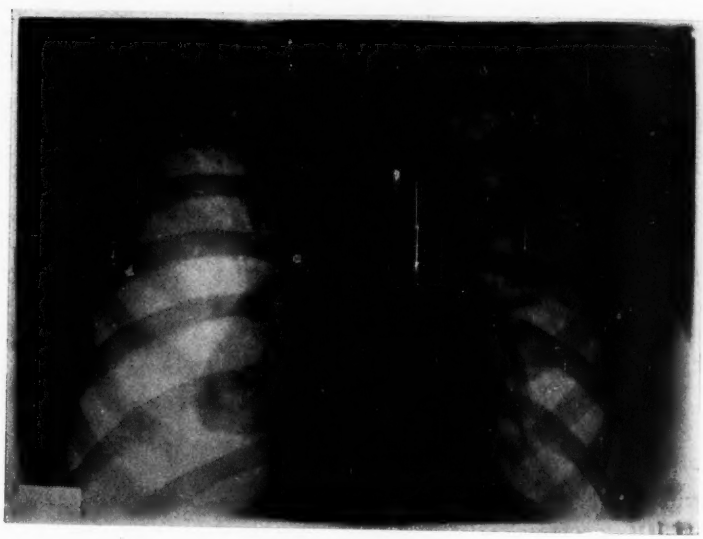


FIG. 2

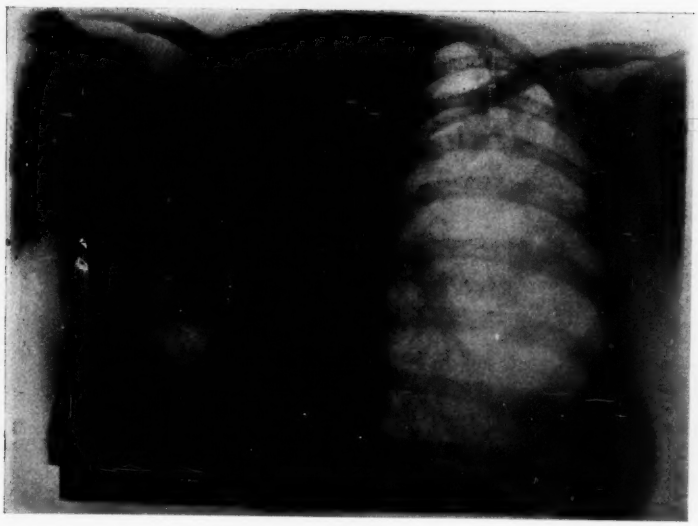


FIG. 3

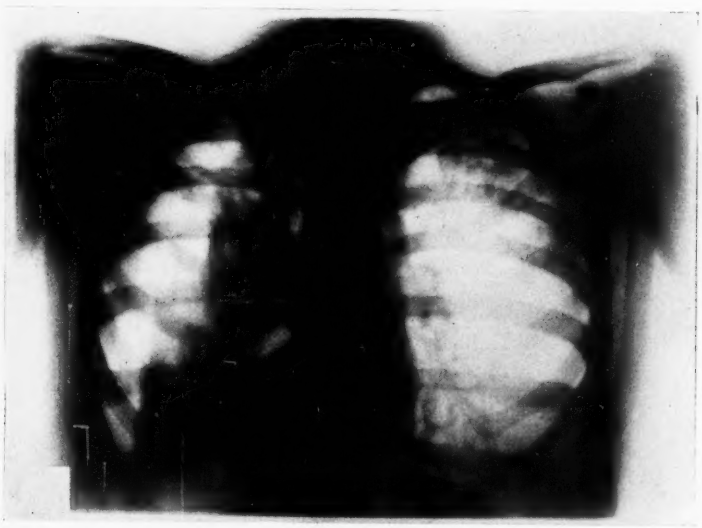


FIG. 4



FIG. 5



FIG. 6

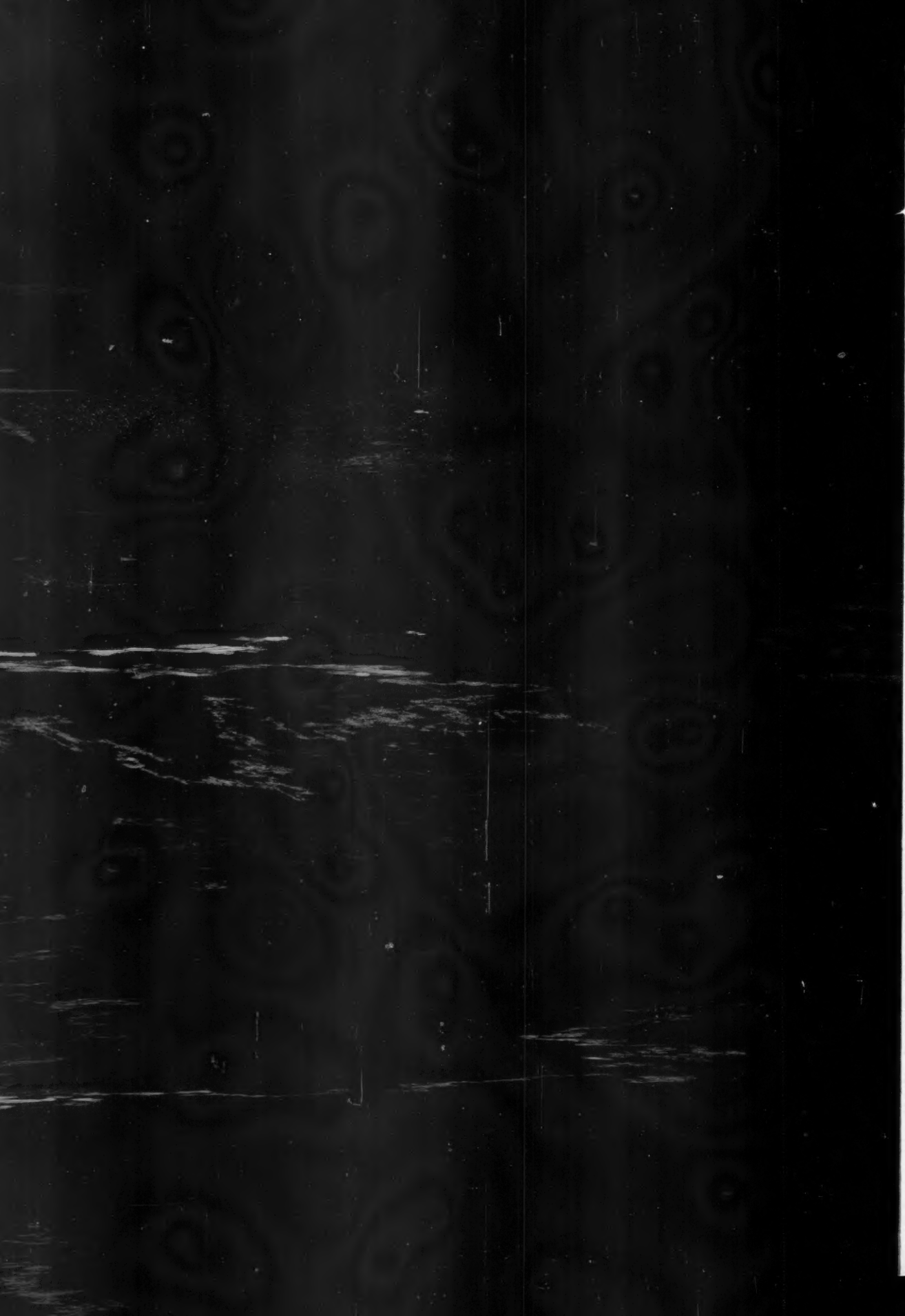




FIG. 7



FIG. 8

THE LOCALIZATION OF FUNCTION IN THE KIDNEY

By W. P. HERRINGHAM and J. W. TREVAN

With Plate 32

The functions of the kidney are little known. The unanswered questions are concerned not only with details, but with fundamental principles. They include such as—

1. What are the forces which cause the production of urine?
2. In what parts of the healthy gland are the various natural constituents added?
3. Is there a relation between special elements of the gland and certain symptoms characteristic of renal disease?

There is no need to recapitulate the familiar story of continued effort directed to answering the first. It is natural to suppose that diffusion takes place in the kidney, but the specialized structure of the various parts, the different proportion of the constituents in the urine and in the blood, and the consumption of oxygen in the kidney, are evidence that secretion is the chief factor. A third force is the pressure of the blood. This, however, must be of moving blood. Ligature of the vein stops secretion. But when the passage through the kidney is free, increase of the blood-pressure, which then produces increase of the blood-flow, causes increased secretion.

Physiology cannot yet tell us how great a part each of these forces plays, nor whether the effect of each is the same or different in kind. It is possible that the excretion of water depends chiefly upon the blood-flow, and that certain salts are separated by diffusion, others by excretion. But this is not as yet certainly known, and it would be useless to recapitulate the numberless theories, and the laborious though inconclusive experiments with which the names of great men have been connected.

It was natural to expect that disease by producing concomitant variations of structure and function would enable pathology to come to the aid of physiology. But pathology has done nothing to settle the fundamental dispute between diffusion and secretion, and the effect of disease, at any rate in man, is so widespread not only in the kidney, but over the rest of the organism, that though one or two types of lesion have been broadly correlated with their main symptoms, no accurate definition has been made, and no one symptom has been assigned without dispute to the lesion of a special tissue.

Of late years another path has been opened. De Bonis (1), Bottazzi (2),

[Q. J. M., July, 1913.]

Heineke and Meyerstein (3), and lastly Schlayer began to attack the problem afresh. Repeated papers have been published by the latter (4) on the variations of renal function produced by experimental and natural lesions. It is agreed by all authorities that chromium salts and corrosive sublimate in moderate doses affect almost exclusively the tubular epithelium. Taking these as examples of tubular poisons, Schlayer and his colleagues found that after an injection of one of them the kidney observed in an oncometer was still capable of contracting and expanding as the blood-vessels contracted or dilated to certain stimuli, and still under Na Cl and caffein presented diuresis. When, on the other hand, arsenic or cantharidin was employed the kidney had entirely lost these powers. He therefore considered these latter drugs to be vascular poisons. To a certain extent he was able to appeal to morbid anatomy to support this division; but he expressly refuses to rely much upon it, since the absence of visible lesion cannot in his opinion be held to prove that function is preserved.

His first conclusions were that water excretion is an office of the vascular, salt excretion of the tubular system.

Turning then to employ foreign substances, he found that the excretion of potassium iodide varied with that of salt, while the excretion of lactose did not. The former, like salt, he considered a tubular, the latter, like water, a vascular product.

The investigation of uranium led him to conclude that renal dropsy might be connected with failure of excretion, but that while the latter was due to some local effect within the kidney, dropsy was the result of widespread lesion of the minute vessels of the skin.

Iodide of potassium and other foreign bodies have long been employed as tests of renal efficiency. The quantitative estimation of water, N, NaCl, and other natural constituents, has been used for longer still. It is worthy of note that the want of correspondence between the results had already led to the belief that the functions of the kidney need not vary as a whole, but that there is division of labour within the gland.

The first four of the following cases were in my wards at the same time, and I therefore, with the help of Dr. Trevan, instituted a series of observations upon them with these drugs. He, working in our pathological laboratory, did the whole of the analyses, while I, in the wards, aided by Dr. Morshead, my house physician, was responsible for the clinical and, in Cases I and VI, the anatomical details.

Case I. Rapid onset, cause unknown, oedema, oliguria, ascites, vomiting. Improvement. Relapse, cause unknown, return of symptoms. Peritonitis, erysipelas, death. No retinitis, no cerebral symptoms, no rise of blood-pressure. Post-mortem, large white kidney.

Albert B., aged 8, was healthy up to Sept. 15, 1912. He had never had any previous nephritis or renal symptoms of any kind; he had never had measles, scarlatina, or diphtheria. So far as his parents could tell he had been exposed to no chill recently.

Sept. 16. His eyelids were noticed to be swollen, but as he seemed otherwise perfectly well he was sent to school as usual, until, when the Saturday holiday

came, Sept. 21, as the face was more swollen, he was brought to the hospital and admitted.

Sept. 21. A well-nourished boy, with oedema in the face, and slightly also in the legs.

His tongue was clean, his appetite good. No vomiting. Lungs natural. Heart not enlarged. Sounds natural. Radial natural. Blood-pressure 105 mm. Hg.

The abdomen was moderately distended, and the umbilicus flat and transversely creased, but no other sign of ascites could be found.

The optic disks, retinae, and retinal vessels were natural.

The urine was extremely scanty, and for the first two days he passed only 4 oz. a day. Diuretin and digitalis were prescribed and he was placed upon milk diet, which included tea, bread and butter, and rice.

For the next few days (Sept. 23–28) the urine increased a little and averaged about 15 oz. a day. But the oedema spread to the hands, arms, and back notwithstanding.

During the next four weeks he was very ill. The urine decreased again so that the average was hardly above 7 oz. a day. Ascites became well marked, and the scrotum and penis were so swollen that they each had to be tapped. Vomiting took place almost daily, and the vomited fluid contained urea, though the sweat did not. He occasionally complained of headache. Hot-air baths and pilocarpine injections (gr. $\frac{1}{6}$) were given regularly, and theocin was substituted for diuretin, but without effect.

On October 28 he began to improve. The urine increased, oedema diminished, vomiting ceased, and he was cheerful. From November 9 to 27 he seemed to be convalescent. The urine was on the average 49 oz. a day; beyond a little pitting over the shins there was no oedema left, and his appetite was excellent. Theocin was omitted on the 18th, and the hot-air baths on the 23rd. On the 29th his weight, which had risen from 4 stone (on admission) to 5 stone on Oct. 12, the period of greatest oedema, had sunk to 3 stone 3½ lb.

But on Dec. 1 it had risen by half a pound, and at the same time the urine showed a tendency to decrease. The following are the figures at this time:

Nov. 23	Urine passed	61 oz.	Weight 3 st. 10 lb.
24	,, ,,	44	
25	,, ,,	62	,, 3 st. 7 lb.
26	,, ,,	52	
27	,, ,,	60	,, 3 st. 4½ lb.
28	,, ,,	36	
29	,, ,,	35	,, 3 st. 3½ lb.
30	,, ,,	31	
Dec. 1	,, ,,	30	,, 3 st. 4 lb.
2	,, ,,	16	
3	,, ,,	26	,, 3 st. 6 lb.
4	,, ,,	31	
5	,, ,,	19	,, 3 st. 7 lb.

By the 10th the oedema had perceptibly increased and vomiting had returned. On the 11th and 12th only 6 and 8 oz. of urine respectively were passed. The old remedies were again begun.

On Dec. 14 the temperature rose to 99·8°, and next day to 100·6°.

On Dec. 17 the abdomen was a little tender and erysipelas was found on the thigh. On the 21st paracentesis abdominis was done and the fluid was found to contain pneumococci. On the 23rd he died.

The following points may be added:

The eyes were observed regularly and showed no retinitis throughout.

Beyond an occasional headache, which was not severe, no cerebral symptoms showed themselves.

The blood-pressure, regularly observed, never rose above 100 mm. Hg after the first observation.

The amount of albumin in the urine varied from day to day in a manner which could not be accounted for. Thus:

Nov. 10	Urine passed		44 oz.	Albumin	0·15 %
11	,,	,,	81	,,	0·12 %
12	,,	,,	42	,,	0·25 %
13	,,	,,	40	,,	0·2 %
14	,,	,,	35	,,	0·4 %
15	,,	,,	26	,,	0·3 %

No casts could ever be discovered in the urine, which, though for a few days in October smoky with blood, was for the most part perfectly clear.

No cause could be discovered for the relapse. The boy had remained in bed throughout.

In the first week of his treatment, while he was passing very little urine, accurate determinations were made of his output of N and Cl in the urine. The articles of diet, which were milk, bread, rice, and butter, were accurately measured each day, and the intake of N estimated from the quantities taken. The faeces were not analysed.

TABLE I.

Date.	C.c. of U.	Total N.	N %.	Total NaCl.	NaCl %.	N intake.	N balance.
Sept. 27	284	4·44	1·56	0·4319	0·1521	7·5975	+3·1575
,, 28	350	3·965	1·133	1·433	0·4095	7·5975	+3·6325
,, 29	400	5·432	1·358	1·497	0·3744	6·2268	+1·7948
,, 30	284	4·527	1·509	0·947	0·3159	6·8260	+2·299

Later during the convalescent period the chloride output was again determined. The diet contained the same substances only, but the amounts were not measured.

TABLE II.

Date.	C.c. of U.	Total NaCl.	NaCl %.
Nov. 11	2,300	4·95	0·2152
,, 12	1,193	2·7916	0·2340
,, 13	1,022	1·3858	0·1356

In both these analyses the Cl is estimated as NaCl.

The microscopic appearances in the kidney were very well marked. The changes were practically confined to two constituents, the convoluted tubes and the interstitial tissue.

The convoluted tubes were everywhere diseased. The epithelium was granular, and when Soudan 3 was employed showed in many places small granules of fat. The edges were ragged, the nuclei often did not stain, and all cell structure was lost. The lumen of the tube was occupied partly by granular material, and partly by round homogeneous bodies of various sizes, which appeared to be erythrocytes partly altered, since the eosin did not stain them so red as those to

be seen in neighbouring blood-vessels, and partly, since many of them were very small, dissolved (Fig. 1).

The tubes of Henle's loop, and the collecting tubes, seemed to be entirely unaffected.

The glomeruli again were free from any disease. In a transverse section of cortex 0·72 sq. cm. large there were 218 of them, all of which were natural. The capillaries of the tuft were indeed full of blood, but that might be an affair of the last few hours alone, and at any rate serves to show that they were well preserved and permeable. There was in no case any inflammation of the capsule or exudation into the space (Fig. 2).

The blood-vessels were natural. There was no endarteritis, and the muscular nuclei were well preserved.

There were, however, here and there small areas of distinct fibrosis. There were at least fourteen such areas, some as large as two or three glomeruli, others only about the size of one, scattered over the transverse section. And besides these there were three or four other larger areas in which the fibrosis spread between the tubes, though never so wide as in the former spots (Fig. 3).

Case II. Rapid onset of amblyopia. No retinal change. Recovery. Chronic nephritis.

Joseph J., aged 54, carman, had had pleurisy and pneumonia many years ago, pains in his joints for twelve years, and 'Bright's disease' seven years ago. He drank to excess. Syphilis was denied.

He was in his usual health when on Nov. 24, 1912, he noticed pain in the eyes after reading, and next morning that his sight was impaired. This increased so rapidly that on Nov. 28 he could only distinguish light from darkness, and he therefore came to the Ophthalmic department. Mr. Holmes Spicer found that he could only distinguish large moving objects, but that except for slight sclerotic change in the arteries the retinae were natural. He was admitted.

A bloated, thick-set man.

Lungs natural. Heart's apex in anterior axillary line, second aortic sound accentuated. P. 80 reg. Pressure 160 mm. Hg. Radial thick and tortuous.

Abdomen natural. Legs not oedematous. Cramps in calves.

Urine at first very scanty, but at the end of a week it rose to the normal quantity. It always contained a slight amount of albumin and a few granular casts were found.

The excretion of urea and Cl were tested on three successive days soon after admission.

Date.	C.c. of U.	Total Urea.	Total NaCl.	NaCl %.
Nov. 30	227	4·7	0·18	0·08
Dec. 1	341	9·5	0·65	0·19
,, 2	994	22·9	3·48	0·35

and again:

Dec. 16 Total NaCl = 3·064.

In these analyses again the Cl was estimated as NaCl.

Vision improved so that on Jan. 14 he could with glasses (+2D) read No. 4 test type. No changes appeared in the retina.

He was discharged in his usual health, with slight albuminuria as before.

Case III. Sore throat, oedema, albuminuria. Fits, probably epileptic. Urine rather large in quantity, of low density. Albuminuria disappeared.

Isabel R., aged 14, a well-grown girl, had had measles and pneumonia seven years previously, but never scarlatina or other illness. She was quite well till four weeks before admission, when she had a sore throat, followed a week later by pain in the upper part of the back, swelling of the face, and later of the arms and legs. There had been no vomiting, headache, or drowsiness. Was admitted on Dec. 6, 1912.

She had oedema of face and legs.

Lungs—some bronchitis.

Heart not enlarged. Rhythm tic-tac. No other change.

Pulse 92, regular. Artery natural.

Abdomen natural.

Ophthalmoscopic appearance quite natural.

The urine was always increased in quantity. For the first six days she passed on the average 83 oz. with a low density (10·05). It contained a small amount, from 0·03 to 0·08 per cent. of albumin, and at first a little blood. She excreted on the average 16·5 grains of urea, which was a full amount for the diet to which she was restricted. On Dec. 15 she excreted, on a milk diet, 3·65 gr. of Cl estimated as NaCl. In January the quantity of urine had fallen to 57 oz. a day, but the density remained the same.

Two days after admission she had a series of severe fits. There was no other sign of uraemia, and the condition did not warrant that diagnosis. I believed them to be epileptic.

By January 18 albumin had completely disappeared from the urine. At no time were casts discovered in it. The blood-pressure on the day of the fits was 146 mm. Hg. On Dec. 14 it was 126, on Dec. 18, 130, and on Jan. 21, 96 mm. Hg.

Copious urine of low density is one of the surest marks of a chronic nephritis with fibrosis, and I at first made that diagnosis. But before her discharge the albumin had completely disappeared, and on consideration of the results of the experiments to be detailed I am inclined to think that the nephritis was transient. Nephritis following upon tonsillitis is more apt to recover completely than are other forms.

Case IV. Pneumonia, nephritis, much haematuria, no oedema. Chronic course.

Arthur W., aged 5, had had measles when a year old, but since then had been in perfect health till Oct. 19, 1912, when he complained of general malaise. For three days he had diarrhoea. On the 24th he shivered, became feverish, and began to cough. He had been in bed since then, and lately the abdomen had swollen. He was admitted Nov. 19, 1912.

The family was very tuberculous, and the boy gave a marked reaction to von Pirquet's test.

He was pale and delicate, had herpes on the lip, and showed signs of consolidation remaining in the right lung. There was slight fever for about a fortnight. The lung eventually cleared up.

The heart was natural, the pulse 112, and it remained at this level after the temperature had fallen to normal.

There was some ascites. A sample of the fluid showed no tubercle bacilli, but a few strepto- and staphylococci. The spleen was at first a little enlarged, but went back behind the ribs in about three weeks. The blood-count was not altered from the normal.

The optic disks, retina, and vessels were natural.

There was no oedema of the skin anywhere.

The urine was remarkably altered. The quantity was somewhat less than normal (20 to 30 oz. daily) throughout. The specific gravity was low, about 1010.

There was during December from 0·2 to 0·7 per cent. of albumin, and much blood. In January the percentage of albumin fell to about 0·15, but there was still a large amount of blood. Casts of all kinds crowded the field.

On one day, Dec. 10, the chloride excretion was determined and found to be 1·199, estimated as NaCl. The boy was on milk diet.

The urine was used to inoculate a guinea-pig on the possibility that the haematuria might be due to tuberculosis, but no reaction followed. The pig was perfectly well four weeks later.

On Jan. 21 the boy was looking and feeling better and the other viscera appeared normal, and in March he was discharged to a convalescent home, but the urine still contains blood and albumin (April 14, 1913). In May he was in the same condition.

Case V. Oedema for nine months, marked on admission, broncho-pneumonia at left base, ascites, much albuminuria with casts, improvement.

Emily F., aged 6, had been quite well until nine months ago, when swelling of all parts of the body and face was noticed. There was at first pain in the abdomen. She had had several fits of drowsiness during this time. Five months ago the Medical Inspector of the school said the kidneys were affected.

No cause could be discovered for the original attack.

Feb. 10, 1913, on admission very oedematous and drowsy: gums bleeding readily, ascites marked.

Broncho-pneumonia at left base.

Heart apparently natural. Retinae natural.

Urine 35–40 oz. (1050–1200 c.c.), acid, specific gravity about 1006, albumin 0·1–0·2 per cent., casts found.

The weight 3 st. 1 lb. rose to 3 st. 3½ lb. (Feb. 13) and then began to fall.

Feb. 17. Saltless diet begun. Weight continued to fall till it reached 2 st. 11 lb. (Feb. 24) and remained steady.

Feb. 27. 5 gr. NaCl given.

March 3. 0·5 gr. KI given. Weight now 2 st. 10½ lb.

March 7. A fish diet was begun and salt no longer debarred.

Albumin was at this time rather higher than at first, viz. 0·3 per cent., with an excretion of 35 oz.

March 13. The weight had risen slightly, to 2 st. 12 lb.

Urine about the same quantity. The albumin had risen at first, but now was 0·24 per cent. A little puffiness of the eyelids.

She was discharged with albuminuria.

Case VI. Occasional lumbar pain and vomiting for six months, sudden blindness of right eye, albuminuric retinitis, cardiac hypertrophy, high blood-pressure, no oedema. Post-mortem, contracting kidney of mixed nephritis.

Louisa W., aged 38, had for the last six months suffered occasional attacks of pain in the back, two or three a week, morning vomiting, lassitude, and general malaise. There were no symptoms before the above date. Ten days ago she became suddenly blind in the right eye. For a few days previously vision in this eye had been hazy.

She was a strong, healthy-looking woman. She had borne seven children, the last five years ago. On no occasion had there been any oedema or other symptoms of renal disease.

Mar. 5, 1913, on admission no oedema.

Right eye blind, cannot distinguish light from darkness. Pupil reacts sluggishly. Left eye vision good. Pupil reacts naturally.

Heart's apex outside nipple line, 5½ inches from mid line. No murmur. Second aortic sound and pulse regular, 90–100. Artery thick. Blood-pressure 210 mm. Hg.

Urine average quantity 50 oz., specific gravity 1006–1012, albumin 0·05 per cent. Casts. No blood or glucose.

Ophthalmoscopic examination (Mr. Jessop and Mr. Spicer): albuminuric retinitis in both eyes, and in right eye marked oedema of the disk and surrounding parts, with diminution of size of arteries, due to obstruction of the arteria centralis.

Arteries of left eye wiry.

Other viscera natural.

The right eye had not recovered vision up to April 2. She had considerable headache and vomiting continued, but she did not appear to feel ill, although in a dangerous condition.

Salt-free diet was started on March 7.

On March 15, 5 gr. of NaCl were given in divided doses.

On March 20, 10 c.c. of a 10 per cent. solution of lactose, sterilized according to Schlayer's method, was injected into a vein of the arm at 3 p.m. The urine was obtained every two hours from that time, and gave distinct reactions at 5, 7, and 9 p.m. At 11 p.m. no lactose was present.

On March 19, at 7 a.m., 2 gr. of potassium iodide were given. The excretion was at first quantitatively estimated.

March 19.	7–9.30 a.m.	Urine 303 c.c.,	a slight trace of KI.
,,	9.30–11.45 a.m.	,, 280 c.c.	0·296 % = 0·0830 gr.
,,	11.45 a.m.–3 p.m.	,, 57 c.c.	0·275 % = 0·0156 gr.
,,	3–11 p.m.	,, 812 c.c.	0·175 % = 0·1421 gr.
,,	11 p.m.–7 a.m. March 20.	,, 60 c.c.	0·376 % = 0·0225 gr.

March 20–21. A small quantity, not estimated.

March 21–25. Small traces each day.

March 26. No trace.

April 6. Vomiting began to be daily.

April 10. Vomited 16 oz., which contained urea. She was collapsed, and the breathing was of the Cheyne-Stokes type. Ten ounces of blood were taken from the arm, and one pint of saline solution injected. The urine for the last week had averaged 60 oz. daily. Cryoscopy of the serum gave $\Delta = 0{\cdot}575°$ C.

April 17. During this week the vomiting had been much less, but she had been more restless, was paler, and looked very ill. The urine had much decreased in amount, but, owing to incontinence, could not be measured. There was considerable diarrhoea. She was rather drowsy, and said that she could not see with either eye.

That day she died.

There were never any convulsions.

Post-mortem. No oedema. Cerebral arteries not abnormal.

Pericardium natural. Heart weight, 16½ oz. Great hypertrophy of left ventricle.

Aorta—some, but not marked atheroma.

The whole of the colon was the seat of recent acute inflammation, with some ulceration in the lower part. A great number of round haemorrhagic spots thickly scattered over the mucous surface.

Kidneys 5½ oz. the pair, capsule adherent, surface mottled with pale circular areas.

Other viscera natural.

Microscopic. The first thing remarked was the difference between the outer and the inner part of the cortex. In the outer third all the tissues, tubular, glomerular, and connective, had undergone a patchy necrosis which had made the tubes and their walls look as if melted together, the blood in them a yellow structureless mass, the glomeruli partly structureless.

This, it should be remarked, cannot have been due to post-mortem decomposition, for the autopsy was made only ten hours after death, and the weather

was cool. The change occupied only the periphery, so that it hardly appears in a transverse section made about the middle of the depth of the cortex.

In the parts whose structure was clear and not thus altered, the following changes were observed:

The convoluted tubes were in many areas full of blood-cells, in others the lumen was occupied by a hyaline plug, in a few the plugs were of granular or cellular débris. Many, on the other hand, were simply dilated, and were lined with flattened epithelium.

Henle's and the collecting tubes, which in transverse sections lie grouped together, and in fibrous kidneys are in fibrous areas, were hardly affected at all.

The glomeruli were not so much diseased as I expected. In a cross-section about the middle of the depth of the cortex, cut parallel to the surface, I found, in an area 0·8 square cm. large, 91 healthy glomeruli, 8 in which part of the tuft was structureless, 6 in which there was some apparently albuminous exudation, and 21 in which there was cellular proliferation and exudation. In no case was there that old-standing organized cellular exudation that I anticipated.

The gravest lesion of all was in the arterioles. I have seldom seen such extreme endarteritis. Arterioles of the middle size, i.e. about 60 μ in diameter, not infrequently had a lumen of only 3 or 4 μ remaining.

The capillaries were everywhere enormously distended with blood.

The following experiments were made upon these cases:

Experiment I. They were first placed upon a diet consisting of milk, a little tea, rice, and bread and butter, both made without salt. The intake of NaCl was thus reduced to a minimum.

In the first four cases this diet was continued for three days. On the fourth day, marked by double lines, 5 g. of NaCl, equivalent to about 3 g. of HCl, were given in divided doses. The output of Cl was estimated daily as HCl by Volhard's method. At the same time the total output of N after removal of albumin was also estimated by Kjeldahl's method.

In Case I no Cl was excreted at all. This is, however, perhaps to be attributed to the pneumococcal inflammation from which he was suffering at the time. We are familiar with the retention of Cl which occurs in pneumococcal inflammation of the lungs, and though I do not know that the same effect is produced by pneumococcal infection elsewhere, it seems possible.

In Case II the Cl excretion seems to have reached the level by the time salt was given, for on the same diet in January the same level was maintained. About one-third of the amount given was on that reckoning excreted on the following day.

In Case III again the Cl excretion seems to have reached the level by the third day. On the day when the dose of salt was given the total quantity of urine was by mistake not noted, so that the total excretion on that day cannot be stated. But nearly the whole of it was excreted on the next day, and judging by the percentage some was also excreted on the day of exhibition. We are therefore justified in thinking that she was able to excrete the whole.

In Case IV very little of the dose was excreted.

In Case V the saltless diet had been continued for a full week before the dose of salt was given. More than half of the dose was excreted on the day of exhibition, and the remainder was nearly completed on the following day.

In Case VI the excretion was imperfect, for the average excretion was in the neighbourhood of 2 g., and only two more grams were excreted on the day of trial, whereas the amount should have been 3 g. I cannot explain the rise seen on the previous day.

But Case I showed during September and November a power of excretion of salt which is greater than I should have expected. Judging from the level reached by the remaining cases, I conclude that in September he was retaining some chloride; but at the same time he was able to pass a solution of the strength of 0·4 per cent. (Sept. 28). In November, though the concentration did not rise so high, yet he was passing as much as 4·95 g. in the day (Nov. 11), which I think is fully equal to the intake.

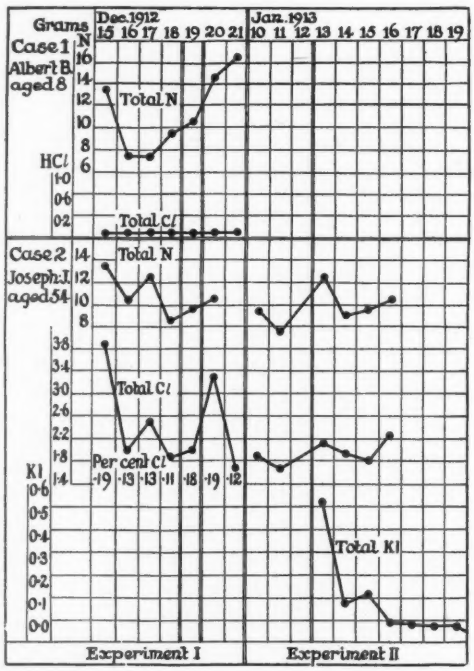


CHART A. Cases I and II. Saltless diet was given throughout the two periods. On Dec. 19, 5 g. NaCl were given in divided doses. On the morning of Jan. 13, 1 g. KI was given.

Experiment II. On the same diet at a later period a dose of potassium iodide was given. In Case II this dose was 1 g., in Case VI 2 g., in the other cases 0·5 g. The urine was tested by extracting the iodine with fuming nitric acid, and titrating the iodine solution with sodium thiosulphate: great care has to be taken that the acid is thoroughly washed away from the iodine solution before titrating. Neglect of this precaution spoilt the first iodine estimation. The chloroform tends to form an emulsion with the urine, and in this emulsion lurks a trace of acid sufficient to make the titration inaccurate. Care should be

taken not to shake the urine more than half a dozen times with each addition of chloroform, and not to titrate till the emulsion has disappeared. With these precautions it is quite easy to titrate within 0·2 c.c. of centinormal thiosulphate (J. T.).

In some cases after the administration of iodide the estimation was made on the specimens of urine as they were voided, in the others on twenty-four-hourly specimens.

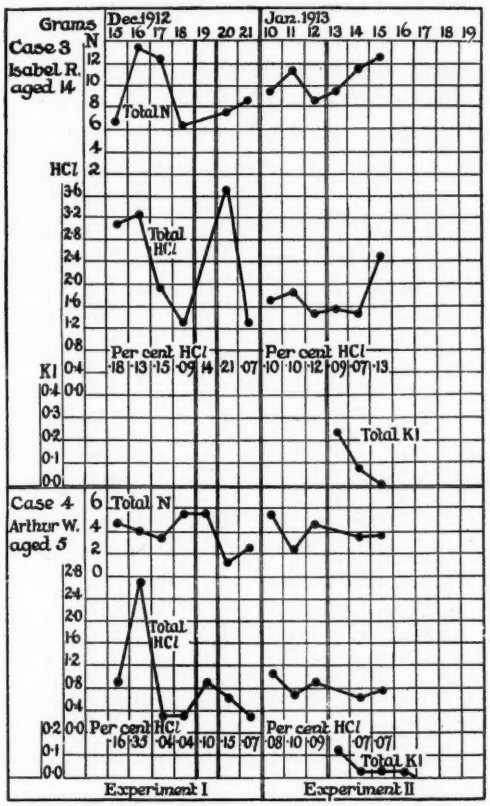


CHART B. Cases III and IV. Same diet and same events as in Chart A, except that the dose of KI was 0·5 g.

In the normal subject the excretion of such a dose should be completed, according to Schlayer's results, in sixty hours or a little less.

In Case II the excretion lasted over seven days. In Case III it was traceable on the third day, but not on the fourth. In Case IV it lasted four days. In Case V it was normal. In Case VI it lasted seven days.

The N excretion, which took place under a diet which for five of the cases was as nearly as possible constant, and for Case V was exactly constant for the whole period, shows remarkable variations. This instability is, however, a regular feature in cases of nephritis.

As already mentioned, Schlayer classes the excretion of NaCl and that of KI together, and ascribes them to tubular activity. Their chemical affinity renders this view the more probable, but they differ in that while NaCl is a normal constituent, KI is a foreign body.

In most of our experiments the two substances are excreted much alike. In Cases II and IV the excretion of each is markedly defective. In Case V it is normal for each. In Case III it is nearly, if not quite, normal for each. But in Case VI, while the NaCl excretion is only slightly affected, that of KI is very inadequate.

There is, however, another point to be noticed. Schlayer remarks that a healthy kidney will excrete an excess of NaCl, if within moderate limits, by merely raising the percentage of its solution in the urine. He reckons it a sign

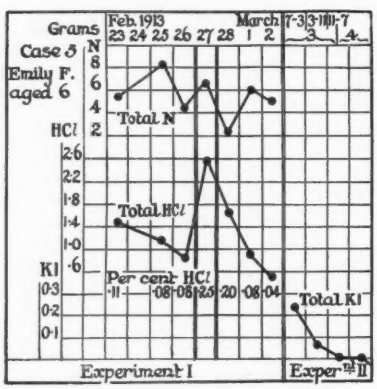


CHART C. Saltless diet was given from Feb. 19 to March 4. On Feb. 27, 5 g. NaCl was given, and on March 7 early, 0·5 g. KI. The first three spaces are 8-hourly periods, the fourth occupies twenty-four hours. Iodine was absent after this.

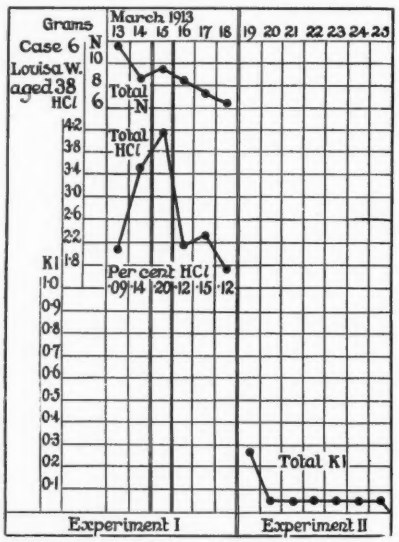


CHART D. Saltless diet from March 7. On March 15, 5 g. NaCl in divided doses. On March 19, at 7 a.m., ½ g. KI.

of failure when the excretion has to be produced by an increase in the urinary water. In Cases III and V the excretion was produced in the normal way by a marked rise in the percentage. In Case II this rise was less marked. In Case VI it was very slight, and in Case IV it hardly occurred.

Turning now to the points which in Schlayer's opinion afford a test of the vascular condition of the vascular mechanism, it is to be remarked that the output of water was very scanty in Case I, and diminished in Case IV. In Cases II and VI it was not sufficiently increased to be significant, but in Case III it was, if the youth of the patient be considered, decidedly above the average.

It is not possible in children to inject lactose into a vein. In Case II, however, a lactose solution properly sterilized, according to Schlayer's method, at

a low temperature, was so injected. The excretion ceased after six hours, which is the mark of a normal vascular regulation. The same occurred in Case VI, which was a typical case of cardio-vascular disease.

It seems, therefore, that while a deficiency of lactose secretion may indicate that the vascular mechanism is affected, although there may be no visible lesions in the vessels or glomeruli, the secretion may be normal in cases where such lesions are well marked. In other words, the coarse lesion of arterial sclerosis is not the form of affection which diminishes lactose secretion.

Apart from the great interest which Schlayer's tests possess as an attempt to estimate separately the degrees to which the tubular and vascular mechanism are diseased, there remains the question how far they are likely to be useful for prognosis.

It is impossible to speak on this point with any certainty. The most that can be done is to say whether or no they are consistent with the opinion which is built upon clinical experience. This opinion is very uncertain. Still it is worth something, and I do not think it will be a waste of time to make the comparison.

In the first place, I should say that my opinion in the first week or two of Cases III and V was worse than the event justified. Schlayer's tests, which were favourable, were better than my judgement. Case IV was a very unfavourable case, and though the boy left the hospital I do not expect him to live long. But here the tests were even more unfavourable than my prognosis. These cases were not tested by lactose, and therefore the tubular mechanism alone was examined.

In Cases II and VI both systems were examined. The prognosis in these two was very different. But the tests give results which are almost identical. Indeed, the salt test is more unfavourable in Case II than in Case VI.

While, therefore, I wish to speak without any attempt to dogmatize, I do not think that in these two cases the tests were of much assistance for prognosis. I hear, however, from Dr. George Graham that Schlayer is now not content with estimating the duration of the lactose excretion, but is also determining the amount of the dose that is passed. This we have not yet done.

The use of the lactose test will, it seems, rather be to show vascular disturbances which we cannot otherwise detect. These I believe with Schlayer to lie at the bottom of dropsy. I have not had the opportunity of tracing lactose on a dropsical case. They are rare in adults.

I believe we do not in our ordinary views allow enough for the effect upon the general system which is produced by the diseased cells of the kidney. I suspect that products are absorbed from them which are very hurtful. In dropsy we seem to see the effect of some product which affects the capillaries almost like an endotheliolysin, and allows the watery part of the blood to permeate through them. In arterial sclerosis there is perhaps another product which affects the endothelium more like an irritant. It may even be some product of cellular disintegration which lies at the bottom of uraemia.

REFERENCES.

1. De Bonis, *Arch. f. Anat. u. Physiol.*, Leipzig, 1906, physiol. Abteil., 271.
2. Bottazzi und Onorato, *ibid.*, 205.
3. Heineke und Meyerstein, *Deutsch. Arch. f. klin. Med.*, Leipzig, 1907, xc. 101.
4. Schlayer und Hedinger, *ibid.*, 1.
5. Schlayer und Hedinger und Takayasu, *ibid.*, 1907, xci. 59.
6. Schlayer und Takayasu, *ibid.*, 1909–10, xcviii. 17.
7. Schlayer und Takayasu, *ibid.*, 1910–11, ci. 333.

DESCRIPTION OF PLATE.

PLATE 32, FIG. I (Case I). (*a*) Convoluted tubule. (*b*) Henle's tubule. (*c*) Collecting tubule.

FIG. 2 (Case I). Normal glomerulus, congested.

FIG. 3 (Case I). A patch of fibrosis.

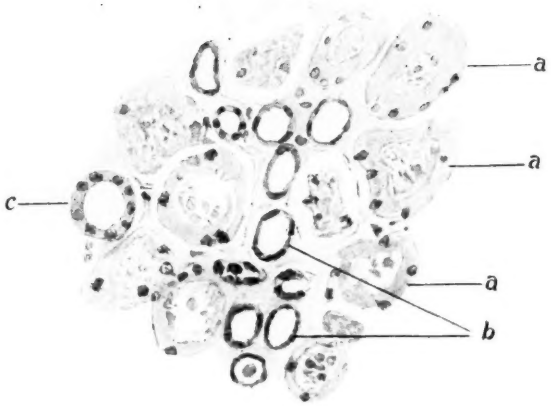


Fig. 1

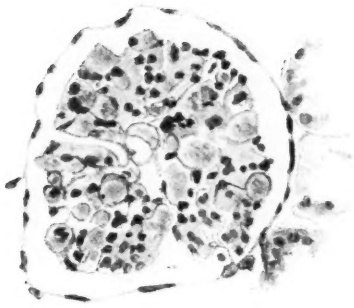


Fig. 2

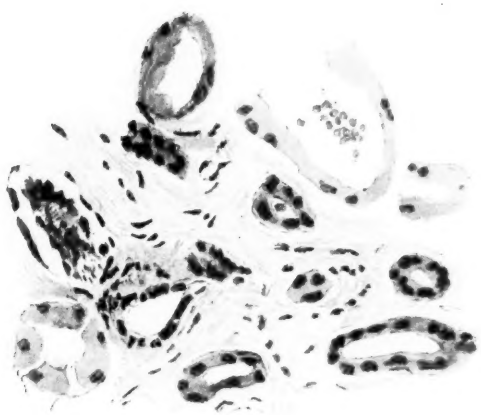
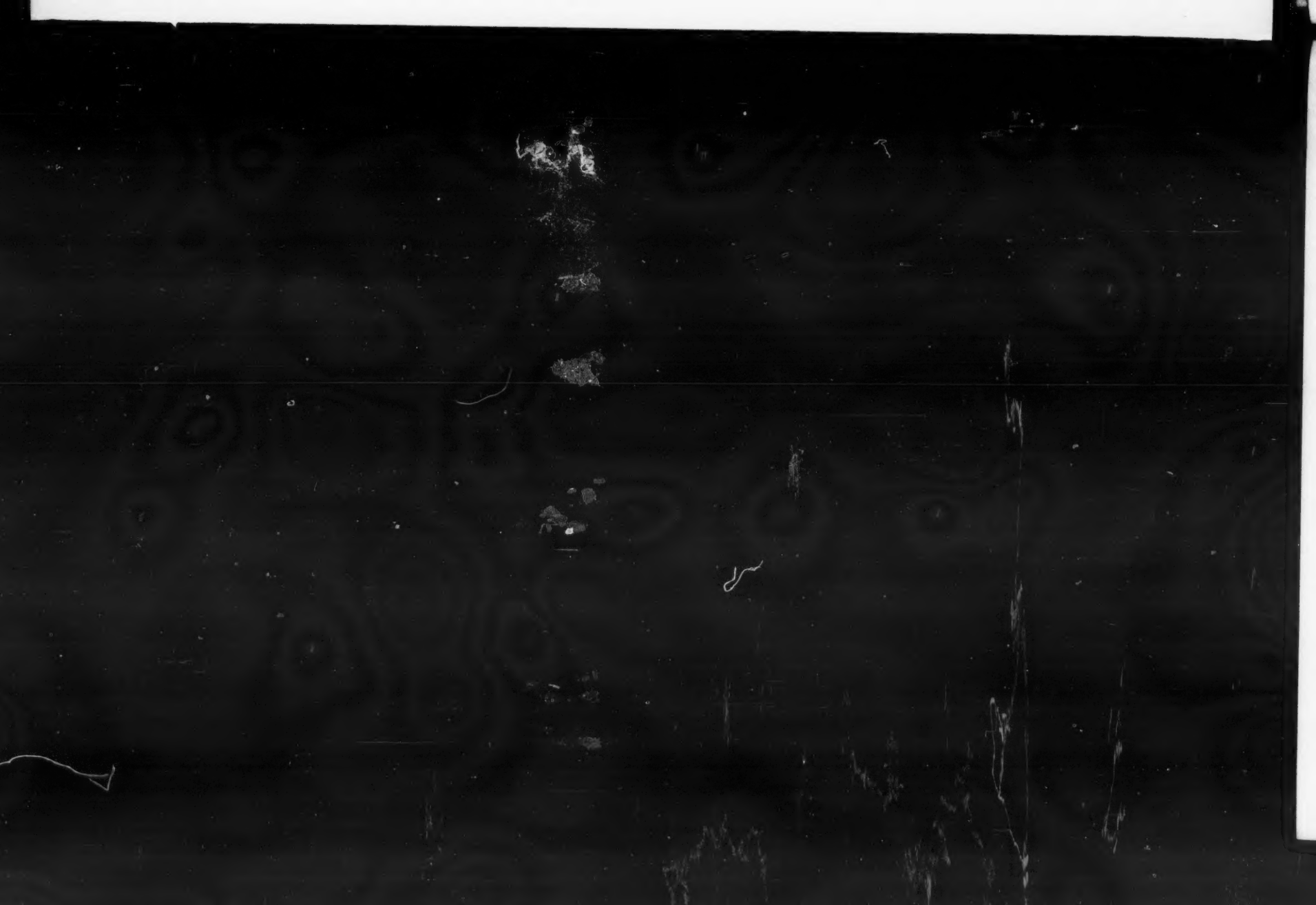


Fig. 3



THE 'SPECIFIC' USE OF SALICYLATE IN ACUTE RHEUMATISM: A CONSIDERATION OF PRACTICAL OBJECTIONS

By REGINALD MILLER

(From St. Mary's Hospital, London)

Of recent years much progress has been made in the study of the problems of acute rheumatism.[1] More particularly have advances been made in our knowledge of its causation, symptoms, morbid anatomy, and histology. But in the matter of treatment, sera and vaccines notwithstanding, we are faced with only one novel conception of importance, namely, that of the 'specific' action of salicylate associated with the name of Dr. David Lees. To me it would appear that it is now necessary that this view should be completely reconsidered; and for two reasons. First, because it cannot be denied that controversy, which has been prolonged and energetic, has tended to obscure the real issues and emphasize in an unwarrantable way one particular point at issue, namely, the dosage of salicylate to be employed. Thus to a large extent the fundamental question of the 'specificity' of the drug has been forgotten. Secondly, reconsideration is necessary and profitable, because the recent histological researches of Carey Coombs (1) have given us an idea of how the rheumatic infection works incomparably clearer than that we previously had. We are able now for the first time to understand, for instance, what a 'specific' anti-rheumatic drug might be expected to do, and what would be beyond its power.

The term 'specific' may be used in various ways, and with one meaning or another there are few who will object to its use in connexion with salicylate and acute rheumatism. But clearly where reference is being made to the action of a drug on an infection, the term 'specific' should imply that the drug has a power of diminishing the activity of the infection by some bactericidal action, direct or indirect. And it is with this meaning that Lees presumably uses the term when he states that 'salicylate is as specific to rheumatism as quinine is to malaria or mercury to syphilis' (3). This dictum, which has been a difficulty to many, can evidently be possibly true only in the sense that salicylate is specific to the rheumatic organism as quinine and mercury are to the protozoon and spirochete of malaria and syphilis. Every one is aware that clinically

[1] In this paper the term 'rheumatism' is used as meaning 'rheumatic infection' and never as synonymous with rheumatic arthritis.

[Q. J. M., July, 1913.]

salicylate often has not the successful action on rheumatism which quinine has on malaria; if it had, as Poynton has remarked, we should have 'recognized it long ago' (5).

The 'specific' view of salicylate in rheumatism must therefore be understood as claiming that salicylate has the power of diminishing the activity of the rheumatic infection, exercising a bactericidal action, direct or indirect. It will be seen that this is a matter of fundamental importance, and it is much to be desired that controversy should be restricted to the elucidation of its truth or the reverse.

It was necessary that I should for my present purposes enter thus far into the theoretical side of the question, but in this paper I do not propose to deal further with this, but to confine myself to certain practical considerations only.

The 'specific' use of salicylate in rheumatism is the practical use of the drug founded upon an assumption of its possessing the antagonistic action defined above. It implies a readiness to employ it freely with a knowledge of its dangers and their safeguards.

In my present paper I am concerned with certain objections which have been raised against the employment of salicylate on these lines. My aim has been to find out to what extent these objections are in fact true; if true, what is their significance, and if they can be overcome.

Records investigated.

For these purposes Dr. Lees most kindly put his hospital records freely at my disposal, and for this generous permission I here return most grateful thanks. These records are unique in the sense that no one has so persistently or for so long employed salicylate as a specific for rheumatism, and are of further interest in that they have not been previously collected and studied. Of these hospital records I studied only those at the Hospital for Sick Children, Great Ormond Street, since it is in children that most difficulties occur. I found that it was during the last three years of Dr. Lees's connexion with the active staff of that hospital that he made the most frequent use of large doses of salicylate and that the records of these details were most accurately kept. I therefore collected all the cases of active rheumatic infection admitted under Dr. Lees's care at that hospital during the three years 1902–4 inclusive, including all cases of arthritis, chorea, nodules, and rheumatic heart disease. Of such there were 152 cases, but of these 28 cases had to be discarded as the records as to treatment were incomplete or else no treatment by salicylate was given.

The remaining 124 cases form the basis of such figures as are given in this paper. In each case salicylate was given for some period, long or short; the dose accurately recorded and vomits charted. The only detail which is not clearly given in all cases is the date of the final omission of the drug. This is

not, however, of much importance, as I know it was Dr. Lees's habit to continue with salicylate well into convalescence and usually until the patient's discharge from hospital.

It is fair to point out that in some of these cases this form of treatment was to some extent experimental, or at all events on pioneer lines. But the importance of the series lies in the fact that all the cases were treated by salicylate and by a physician ready to push the administration of the drug up to the limits of tolerance. It may, however, be a matter of surprise to some to see how comparatively few patients were treated with doses of any sensational size. The preparation used was in practically every case sodium salicylate, combined with a double dose of sodium bicarbonate. The poisoning symptoms of salicylate, particularly those of acid intoxication, were evidently beginning to be recognized (published by Langmead (2) in 1906), but possibly the importance of the avoidance of constipation had not been fully recognized at that time.

Practical Objections.

The views propounded by Dr. Lees have not met with general acceptance; nevertheless I think it is beyond dispute that salicylate is more freely used than formerly. Probably many regard salicylate as a 'specific' without recognizing altogether to what they are committing themselves. On the other hand, it is notorious that several of those most deeply interested in rheumatism are strongly opposed to this view.

I am not here, however, concerned with whether the 'specific' view is right or wrong, but with certain objections which have been urged against its practical application. I must, however, allude where necessary to the relation of the practical objection to the theoretical conception.

Nearly all the objections which I shall notice will be found in the reports of the discussions on the treatment of rheumatism which have taken place of recent years (6). In a few cases, however, I do not know that the objection has actually found its way into print; if so, it has been gathered in conversation with others, and, I hope, fairly expressed here.

I. *Irrelevant Objections.*

I venture to think that numerous objections raised to the specific use of salicylate are founded on unsound views: sometimes upon a misconception of what is meant by the specific action of salicylate, sometimes upon a lack of appreciation of the true symptomatology of rheumatic infection. These I consider first.

We may surely now disregard as irrelevant arguments based on statistics dealing with the development or disappearance of cardiac bruits in numbers of rheumatic cases under this or that line of treatment. The pleading fails because we are not able to correlate the variations in these sounds with the

activity of the rheumatic infection in a series of cases, other details being omitted; and therefore such an argument does not touch the question as to the power of salicylate to diminish the activity of the infection.

Again, statistics giving the period of in-patient treatment in cases of chorea are of no value with regard to the efficacy of salicylate. Such figures are entirely vitiated by such factors as the state of the heart, the severity of the attack, the personal predilections of the physician, the pressure on hospital beds, the facilities for convalescence outside the hospital; while the difficulty of dating the cure of a case of chorea is notorious. But apart from these points, to note merely the average length of time of in-patient treatment is to neglect the crux of the matter. For the centre of the dispute is not the return of the patient to health, but the subsidence of the activity of the infection. It is not too much to say that a failure to appreciate the difference between an active rheumatic infection and the results of a past rheumatic infection (one no longer active) destroys the value of a great deal of what is said or written concerning the salicylate treatment of rheumatism.

Then again, many of the objections urged against the specific use of salicylate in rheumatism are founded upon an imperfect knowledge of the symptoms of that infection; e.g., that salicylate is responsible for such symptoms in rheumatic children as mental depression, cardiac depression, anaemia, headache, albuminuria, and haematuria. These, as rheumatism has been more closely studied, have been found to be symptoms of that infection and not necessarily or even usually dependent upon the line of treatment adopted. Possibly some of these objections have another origin in the use of an impure preparation, such as was commonly obtained years ago, but rarely met with now. I need not deal with these points in detail since they have been generally met by others, and I will merely take one symptom, that of mental depression, to show in what way the confusion has arisen.

In a study of the mental symptoms of rheumatic children a few years ago (4) I emphasized the fact that during the acute stages a child was mentally depressed, just as surely as it becomes mentally exalted in convalescence. Both these mental pictures are found equally in those taking and in those not taking salicylate; they are symptoms of the infection. But confusion arises from the fact that it cannot be denied that if a child is allowed to be nauseated by salicylate, the drug becomes responsible for added mental depressive symptoms. Such a result is due then to the injudicious use of the drug, and experience clearly shows that it is not simply a matter of the amount of the drug given.

II. *Relevant Objections.*

I come now to the consideration of certain objections to the practical use of salicylate as a specific anti-rheumatic which are of importance, in that if, and as far as, they are true, they militate against this use of the drug. I cannot here consider all such objections that have been raised, but must refer to a few

which have not yet been properly studied; and I shall endeavour to show what truth they contain, what they signify, and if they can be avoided.

The objections which I propose to consider are the following:

(i) Absorption of salicylate: That the larger doses implied in the 'specific' use of salicylate are of no value, since they are either not absorbed or, if absorbed, produce toxic symptoms;

(ii) Vomiting under salicylate: That the larger doses of salicylate are undesirable owing to their frequent production of harmful vomiting;

(iii) Acid intoxication under salicylate: That these doses are undesirable owing to their frequent production of dangerous symptoms of acid intoxication;

(iv) Fatalities under salicylate: That the larger doses are harmful and may actually cause death in rheumatic cases which would not otherwise have died;

(v) Relapses under salicylate: That the specific use of salicylate is unsound as it does not prevent relapses; particularly the development of nodules.

It is very evident that such objections as these are most important, and that no clear ideas as to the action of salicylate as a specific for rheumatism can be formed until these have been examined. The rest of this paper is concerned with their consideration, based upon an examination of the clinical material to which I have already alluded.

(i) *Absorption of Salicylate.*

The suggestion is that large doses of salicylate are of no value as they either remain unabsorbed and are evacuated by the bowel, or if absorbed produce toxic symptoms. This objection rests on two considerations: first, that acid intoxication is largely a question of the amount of the drug given, and secondly, that constipation conduces towards acid intoxication by increasing the amount of salicylate absorbed.

To answer this objection the following arguments may be brought forward:

(*a*) While it is certain that constipation during salicylate treatment greatly increases the liability to acid intoxication, it is by no means certain that it does so merely by increasing the amount of the drug absorbed; for, as will be shown later, the dose employed is not a matter of supreme importance, cases of acid intoxication arising on small or large doses where constipation is present. It is possible that constipation predisposes towards acid intoxication with salicylate in the same obscure way as it predisposes towards a similar condition in diabetes.

(*b*) Be this as it may, it does not follow that with large doses well tolerated, a larger amount of the drug is not absorbed. This conception would presuppose the evacuation of all harmful excess, a beneficent mechanism which is not known to act in the case of other poisons.

(*c*) By analysis of the urine it can be clearly shown that the larger the dose the more of the drug is absorbed, even in the absence of constipation. Mr. J. Webster, Demonstrator of Chemical Pathology at St. Mary's Hospital Medical School, kindly investigated this matter for me in a series of in-patients under my care. In each case, before the urine was analysed, the patient had been taking the same dose of salicylate for at least three days, and in no case was there vomiting, constipation, or signs of poisoning. The following figures refer to the grains of sodium salicylate taken in twenty-four hours and approximately the number of grains of salicylic and salicyluric acid (calculated as salicylic acid) passed in the urine during the same twenty-four hours.

Grains taken.	Grains in urine.
90	28
150	46
200	80 (average)
250	112

The same methods of estimating the salicylic and salicyluric acid in the urine were used in each case. Mr. Webster does not regard his figures as entirely exact, but is assured that the error is too small to negative their being conclusive for my present purpose.[2]

These figures show clearly that an increased dose implies increased absorption in the absence of constipation or toxic symptoms. There does not, therefore, appear to be any weight in the objection considered here.

(ii) *Vomiting under Salicylate Treatment.*

This objection may be broadly stated thus: that the use of salicylate as a specific for acute rheumatism is not practicable, inasmuch as the drug in large doses is too prone to produce harmful vomiting. This is an important objection as it rests upon the undoubted fact that salicylate has an irritant effect on the stomach which is probably diminished, but not annihilated, by the simultaneous administration of alkalis. *A priori*, therefore, we should expect the larger doses to increase the tendency to vomiting.

We have here, therefore, to examine Dr. Lees's cases to ascertain the amount of vomiting which occurred during the administration of salicylate; to trace the relationship of this vomiting to the dose employed or to any other factors which may appear to be of importance.

(*a*) *Amount of vomiting. Vomiting not due to salicylate.* Rheumatic children may vomit when no salicylate is being given. The common causes are the initial purge and cardiac dilatation. In the present series of 124 cases,

[2] Mr. Webster hopes to continue these investigations in order to obtain greater accuracy in the estimation of salicylic and salicyluric acids in urine.

11 (8·87 per cent.) vomited from these causes; the amount of vomiting ranging from 1 day to 19 days.

Vomiting due to salicylate. In determining the amount of vomiting due to salicylate I have included all vomits which occurred while the patient was taking salicylate as 'due to' the drug; also I have included all vomits which occurred after salicylate had been withdrawn, but apparently due to its previous administration. My figures may therefore be taken to represent the maximum.

No vomiting under salicylate. Of the 124 cases, 68 (54·83 per cent.) did not vomit at all while undergoing salicylate treatment.

'Slight' vomiting under salicylate. In this group I have placed such cases as did not vomit on more than four days during their course of treatment, in whom the salicylate, if omitted at all, was withdrawn only once and resumed without further difficulty, and in whom the vomiting did not appear to be harmful and gave rise to no anxiety.

In this group are 44 cases, representing 35·5 per cent. of all cases under treatment, and 78·6 per cent. of those cases which vomited. The greatest number of vomits for one case was 8, occurring over 4 days; and the average number 2·5 vomits per case. The average duration of each child's stay in hospital was 49·79 days.

In most of these cases (36 out of 44) the vomiting was quite trivial, the drug not having to be omitted. Generally (26 cases) it occurred at the beginning of the treatment or on increasing the dose. In the others (10 cases) it occurred when the child had been taking the same dose for some days, and ceased without alteration in the dose. In the majority of these cases only one vomit occurred. Constipation was traceable in some of these, and also in two cases where the vomiting extended over two or three days.

In three cases there was great cardiac dilatation. All these were fatal cases and will be dealt with when the mortality is considered. One died on the fourth day of in-patient treatment; the other two vomited both with and without salicylate.

In five other cases the salicylate was omitted on one occasion for periods of 12 hours to 3 days, and then resumed without provoking further vomiting. Here the drug must be held responsible for such vomiting as occurred, but no real difficulty was experienced in carrying out the treatment.

'Serious' vomiting under salicylate. In this group I have placed all cases in which vomiting occurred under salicylate on 5 days or more. Of the 124 cases, 12 come under this heading, representing 9·67 per cent. of all cases under treatment, and 21·42 per cent. of those which vomited. Vomiting occurred on an average of 9 days per case, with an average of 16 vomits. The average duration of each child's stay in hospital was 70·25 days.

These are the important cases. In order that the exact part played by the drug may be estimated it is necessary that they should be studied in detail. The table with the notes that follow will enable this to be done.

TABLE I.

'Serious' vomiting under salicylate: to be read with notes following. N.B.—The dose of salicylate in col. 5 is the maximum daily dose in grains which produced vomiting; not necessarily the maximum dose given, nor the dose on which most vomiting occurred.

Case No.	Age.	Admitted for:	Heart Disease.	Maximum Dose with Vomiting. Grains.	Vomiting.		Days in Ward.	Result.	Predisposing Cause of Vomiting under Treatment.
					Days.	Vomits.			
78	9	Arthritis	Slight to Severe	60	7	12	33	Died	Partly cardiac
92	9	Heart	Severe	80	14	32	117	Died	Cardiac
94	9	Heart	Severe	80	7	11	156	Improved	Cardiac
100	7	Heart	Severe	120	13	26	42	Improved	Cardiac
109	6	Heart	Severe	350	9	27	94	Improved	Cardiac + Dose
112	11	Heart	Severe	150	5	8	61	Improved	Cardiac
117	7	Heart	Severe	200	10	14	63	Improved	Cardiac
118	4	Heart	Severe	100	8	12	63	Improved	Cardiac
70	10	Chorea	Slight	150	7	12	42	Improved	Acidosis
99	11	Heart	Severe	120	5	8	56	Improved	Acidosis
89	6	Chorea	Slight	300	8	8	53	Improved	Dose
59	9	Chorea	Slight	200	16	24	63	Improved	Idiosyncrasy

Examining these twelve cases of serious vomiting under salicylate treatment we find that in eight instances there was present severe cardiac dilatation. This, as I show in the section dealing with vomiting in relation to the type of rheumatic case under treatment, is a powerful predisposing factor to vomiting. The exact influence of the salicylate on the production of the vomiting can be judged from the following notes:

Case 78. Admitted for arthritis and slight heart disease. Vomited second and third day on 60 gr.,[3] and on fourth day on 40 gr. No further vomiting on this dose; omitted tenth day. Seventeenth day pericardial friction. Twentieth day 60 gr. given and continued until death. Vomited twenty-first and twenty-fourth days; leeched twenty-first day. Friction gone twenty-sixth day. Chorea developing; pain in fingers twenty-eighth day. Temperature came down thirtieth day; gradual improvement; sudden death thirty-second day (*v.* Fatal Cases).

Case 92. Large heart, mitral, systolic, and presystolic; much bronchitis. Post-mortem: mitral, aortic, and tricuspid endocarditis; pulmonary infarction. Much vomiting throughout. Salicylate not given regularly; on salicylate 50 days, vomited 14 days (32 vomits); off salicylate 67 days, vomited 19 days (31 vomits). Maximum dose given 80 gr. daily.

Case 94. Heart much dilated; one nodule; did not vomit when not taking salicylate.

Case 100. Heart much dilated; cardiac symptoms; nodules. Vomited much on 60 and 120 gr.; less on 40 gr. of salicin.

[3] Throughout this paper the dose given is the number of grains given in 24 hours; the drug used, unless specially mentioned, was sodium salicylate; it was always combined with a double quantity of sodium bicarbonate. The daily dose was usually subdivided into 10 doses, given 2-hourly during day, and 4-hourly during night.

Case 109. Heart much dilated; vomited much on 100 gr. As heart improved vomiting ceased without reduction of dose. Dose then increased to 350 gr., which were well taken for 10 days. Then vomiting again without great cardiac dilatation. Child only six years old.

Case 112. Severe old heart disease with acute pericarditis; leeched first and tenth days. Vomiting before salicylate given; ceased while taking 200 gr.

Case 117. Heart much dilated; nodules. Vomited as dose increased. Drug temporarily omitted four times.

Case 118. Heart much dilated; nodules developed. Salicylate not much given, chiefly 50 gr. for 3 days at a time. Constipated.

In the above 8 cases, only 2 vomited while not taking salicylate. This proves that in many cases of severe cardiac dilatation the drug itself is the exciting cause. But as regards the influence of the size of the dose of the drug we get indications of what will be shown to be the case later (*v.* Relationship of vomiting to dose employed), namely, that it is of secondary importance to the condition of the heart. In 3 cases (Nos. 78, 92, 94) the dose employed was comparatively small; in Cases 100 and 118 most of the vomiting occurred on 60 gr.; in Cases 109 and 112, as the heart improved the vomiting ceased without reduction in the dose of salicylate (100 gr. and 200 gr. respectively). Case 109 shows that a child of six can take the enormous dose of 350 gr. per diem for 10 days without vomiting if the heart is not much dilated. On the other hand, the occurrence of vomiting with successive increments in the dose of salicylate (Case 117) suggests that the size of the dose has an influence, as indeed it must have, since the drug is a gastric irritant.

These considerations therefore foretell what will be discussed later, that the condition of the heart is a most important factor, and, speaking generally, the more dilated the heart, the less salicylate can be given without producing vomiting.

In two of the remaining cases acid intoxication developed. In both there was no action of the bowels charted during the two preceding days. These will be discussed under acid intoxication.

Case 70. Admitted for chorea and slight heart disease. Acid intoxication developed on the third day of taking 150 gr.

Case 99. Admitted for mitral and aortic regurgitation; nodules. Vomited the first 2 days on 120 gr. of sodium salicylate. Later developed air-hunger and vomiting on 120 gr. of aspirin.

In the eleventh case of 'serious' vomiting the size of the dose appears to have been entirely responsible, a very large dose for the age of the child being given.

Case 89. Aged 6. Admitted for severe chorea and slight heart disease. Vomited after increase of dose, salicylate omitted for 3 periods of 24 hours. Dose increased to 300 gr.

The last case appears to have been one in which the child (a Russian Jewess, aged 9) could not or would not take salicylate well. Vomiting occurred at various doses, such as are usually well tolerated. Although I have no great liking for the term 'idiosyncrasy against salicylate', this case may be regarded as an example of what is usually meant by the phrase.

Case 59. Admitted for chorea and slight heart disease. Vomiting occurred at various doses, which were at one time increased to 200 gr.

The amount of vomiting occurring under treatment by salicylate in the series of cases examined may be summarized in the following table; vomiting was absent or slight in 90·32 per cent. of cases.

TABLE II.

Summary of amount of vomiting under salicylate treatment (124 cases).

Vomiting.	No. of Cases.	Percentage.
None . .	68	54·83
Slight . .	44	35·5
Serious . .	12	9·65

(*b*) *Relationship of vomiting to dose employed.* In presenting figures on this point a difficulty arises in that the maximum dose administered and the maximum dose producing vomiting were not always the same. Many cases took a larger dose than the largest producing vomiting. Thus in 8 cases 50 gr. or less was the largest dose given, but in three others this was the largest dose producing vomiting, larger doses being tolerated well. In order to overcome this difficulty as well as I can, I consider first the number of cases in which no vomiting occurred, grouping them under the maximum daily dose (Table III).

In studying the relationship of the dose to the number of cases of 'serious' vomiting another difficulty arises in the fact that much of the vomiting may have occurred at a lower dose than the maximum under which the case is classed. Thus, Case 109 vomited chiefly on 100 gr. and took 350 gr. fairly well; in Case 118 nearly all the vomiting occurred on 50 gr. daily, 100 gr. being given for one day only. To minimize this inaccuracy I have inserted in Table III the case-numbers of the examples of serious vomiting, so that reference may be made to Table I and the notes following it.

TABLE III.

Showing relationship of maximum dose to percentage of cases not vomiting, and with 'serious' vomiting.

Max. Dose daily. Grains.	Cases.	No Vomiting.	Percentage.	Serious Vomiting (with Case-numbers).	Percentage.
1–50	8	4	50	0	0
51–100	38	22	57·8	4 (78, 92, 94, 118)	10·5
101–150	36	25	69·4	4 (59, 70, 99, 100)	11·1
151–200	22	10	45·4	2 (112, 117)	9·0
201–250	4	1	25	0	0
251–300	12	6	50	1 (89)	8·3
301–350	2	0	0	1 (109)	50·0
351–400	2	0	0	0	0

Since salicylate is a gastric irritant, it must be supposed that to increase the dose is to add to the tendency to produce vomiting. With this in mind it is interesting to note in Table III that the percentage of cases not vomiting does not tally closely with the dose employed, nor does the percentage of cases showing serious vomiting increase steadily with an increase of the dose. Further, it is very striking that the range of dose (51–150 gr.) in which the percentage of cases not vomiting is highest, is the range within which three-quarters of the cases of serious vomiting fall.

One can therefore conclude that the size of the dose of salicylate is not the most important factor in producing vomiting in clinical work.

(c) *Relationship of vomiting to type of rheumatic case.* Inquiry into this matter elicits one interesting point. Analysing and subdividing rheumatic cases as one will, one cannot correlate a marked tendency to serious vomiting under salicylate treatment with any type of case except one, namely, where the heart is much damaged. This is as might be expected, since cardiac dilatation is well known to predispose towards vomiting.

Vomiting in severe heart disease. In the twelve examples of serious vomiting during salicylate treatment we saw (Table I) that in eight there was cardiac dilatation of severe degree.

Analysing the series of 124 cases for cases of severe heart disease, I find that the heart was dilated two or more finger-breadths outside the left vertical nipple line, with or without acute pericarditis, in twenty-four cases; while in three others the heart was severely enlarged from the presence of endocarditis of two or more valves. Thus twenty-seven cases may be regarded as instances of severe heart disease. In these twenty-seven cases there are eight examples of serious vomiting, representing a percentage of 29·62; while vomiting was absent or slight in 70·37 per cent. of this group.

Subtracting these twenty-seven cases from the total series of 124, there are left ninety-seven cases in which there occurred four cases of serious vomiting (4 per cent.), and reference to Table I shows that of these four cases, two (Nos. 70 and 99) were associated with constipation and acid intoxication, one (No. 59) with idiosyncrasy, and one (No. 89) with what was apparently too large a dose for the age of the child. In Case 109 vomiting was due mainly to cardiac dilatation but also, later, to an overdose.

The extreme importance of cardiac dilatation as a predisposing factor to vomiting under salicylate is seen in Table IV, where the great increase in the percentage of serious vomiting amongst such cases is seen.

TABLE IV.

Showing the great increase in the percentage of serious vomiting among cases showing severe heart disease.

Cases.	No.	Vomiting slight or absent.	Vomiting serious.
All cases . . .	124	112 (90·3 %)	12 (9·6 %)
Without severe heart disease . . .	97	93 (96·0 %)	4 (4·0 %)
With severe heart disease . . .	27	19 (70·3 %)	8 (29·5 %)

Severe cardiac dilatation is of course well known to be associated with a tendency to vomiting, and the question arises as to how far the administration of salicylate may determine the onset of vomiting here. Table V illustrates this point, and shows that in 40 per cent. of the cases of severe cardiac dilatation vomiting occurs only while salicylate is being given; while another 40 per cent. will take the drug well, and a small number vomit with or without salicylate.

TABLE V.

Influence of salicylate in determining vomiting in 27 cases of severe heart disease.

	No. of Cases.	Percentage.
No vomiting with salicylate .	11	40·74
Vomiting with and without salicylate	4	14·81
Vomiting only without salicylate	1	3·7
Vomiting only with salicylate	11	40·74

Vomiting under salicylate: Summary. In cases of active rheumatism in children treated freely with salicylate, vomiting may be expected to be troublesome in about 10 per cent. of all cases; excluding cases of severe heart disease this figure is diminished to about 4 per cent.; counting only cases of severe heart disease, it is increased to 30 per cent. Of the last group, while about 40 per cent. take the drug without vomiting, a similar number vomit only while receiving it, while some vomit with and without salicylate.

Salicylate is a gastric irritant, and therefore increasing the dose must increase the tendency to vomiting. In practice, however, the influence of the size of the dose appears to be counterbalanced by other factors, the chief of which are the avoidance of acid intoxication (*v. infra*) and the condition of the heart.

Where acid intoxication is avoided and where the condition of the heart is satisfactory, very large doses, such as 350 gr. for a child of six years, can be tolerated for a week without producing vomiting. But it is evident that the great tendency to vomiting shown in cases with severe cardiac dilatation must tend to limit the specific use of the drug as an anti-rheumatic in cases of active cardiac rheumatism.

(iii) *Acid Intoxication under Salicylates.*

The objection to the specific use of salicylate on this score is that large doses are too prone to cause acid intoxication to be safe.

There are two undoubted cases of acid intoxication in the present series of 124 cases (Cases 70 and 99). The symptoms here were in both cases preceded by two days on which the bowels did not act. In one the patient was taking 150 gr. of sodium salicylate and 300 gr. of sodium bicarbonate; the doses having been raised to these figures two days previously. The other case developed acid intoxication on 150 gr. of aspirin daily. In both cases drowsiness, vomiting, air-hunger, and acetonuria were present. The symptoms lasted about forty-eight hours and the after progress was satisfactory.

In one other case there developed delirium and acetonuria, but without air-hunger or vomiting, on 200 gr. of salicylate daily, preceded by two days' constipation. This may perhaps have been one of those peculiar cases which are seen from time to time, in which drowsiness, delirium, and possibly rigidity develop without vomiting or air-hunger. The clinical condition resembles an early tuberculous meningitis rather than the ordinary picture of acid intoxication; nevertheless when it is examined for, acetone is found in the urine. It is difficult to say if such cases as these are due to salicylate poisoning, as the ordinary cases of acid intoxication developing under salicylate undoubtedly are. From their occasional occurrence in little groups of cases it would appear that they are connected with the administration of the drug and are possibly due to some impurity. But as their cause is not very clear they are for safety to be regarded as examples of salicylate poisoning. For this reason this third case is included here.

When it is considered that this series of cases was treated at a time when the true symptoms of salicylic acid poisoning were only just being appreciated, it cannot be said that three instances in 124 cases is an alarmingly high proportion; while it is to be noted that evidently the large doses themselves are not entirely responsible for the condition, as no case developed amongst those treated with the largest doses of salicylate.

With so few cases in the present series I must draw upon other instances which I have had the opportunity of watching, and in the light of these I am of opinion that acid intoxication need never be allowed to develop under treatment by any reasonable dose of salicylate, say 250 gr. per diem. It is certainly not only due to the size of the dose, for I have seen it develop many times in children taking only 60 gr. daily, and seen others taking 400 gr. daily with no symptoms of acidosis. It can be prevented by observing the following three points:

(*a*) Constipation must be prevented; particularly the dose of the drug should not be increased if constipation be present. With constipation acid intoxication may develop on quite small doses, even 15 gr. daily, and is not

uncommon on such ordinary doses as 60 gr. daily. I do not think that the constipation acts merely by increasing the amount of the drug absorbed, as I have already discussed in Section (i) of this paper.

(*b*) The urine should be kept alkaline or neutral. In order to do this Dr. Lees was accustomed to combine a double dose of soda with the salicylate. I have not found it necessary to give more than equal doses of soda in administering salicylate up to the dose of 250 gr. daily, beyond which I have never had occasion to go in my own practice. Even a double dose of soda will not keep the urine alkaline if constipation be present, while an equal amount of soda with the salicylate appears sufficient if constipation be prevented. Aspirin, which cannot be combined with soda, is less suitable from this point of view than sodium salicylate.

(*c*) The salicylate should be given in small doses frequently, most conveniently in ten doses in the twenty-four hours, as recommended by Dr. Lees. To try to give a daily dose of 150 gr. divided into only three or four doses is to court vomiting and severe symptoms of poisoning.

Acid intoxication: Summary. Acid intoxication is a real danger in the use of salicylate, but it does not particularly militate against the use of large doses. It arises much more from the method of administration than the size of dose, and there is now no reason why such symptoms should be allowed to develop under salicylate treatment.

(iv) *Fatalities under Salicylate.*

This objection is to the effect that salicylate, particularly in large doses, is prone to do harm in various ways, so that it tends to increase rather than diminish the number of fatal cases of rheumatism.

This objection is not often to be found in print, but I have frequently heard it in conversation, and it is probably more frequently held than expressed. It is of course a legitimate and most important objection. It must be remembered in this connexion that where a physician is known to be particularly interested in such a common disease as rheumatism he is likely to have his wards pretty full of examples of every degree of severity. Further, that when he is known to recommend very large doses of salicylate, it is assumed at every autopsy on one of his rheumatic patients enormous doses have been used.

I here therefore examine the 124 cases under Dr. Lees's care in order to ascertain if the death-rate was particularly high; if any fatal cases could be attributed to the treatment by salicylate, particularly to large doses. For these purposes each fatal case must be considered separately.

In the series of 124 cases there were six deaths. In one of these the cause of death was diphtheria and broncho-pneumonia. Neither rheumatism nor salicylate contributed to the fatal issue.

Case 77. Girl, aged 10. Slight chorea, slight cardiac dilatation. Given sodium salicylate for thirteen days; maximum daily dose, 120 gr.; no vomiting.

Then given arsenic. Twenty-first day, B. diphtheriae in throat and broncho-pneumonia. Twenty-third day died. *Post-mortem*: No endocarditis; myocardium pale; broncho-pneumonia; B. diphtheriae found.

Excluding this case, there were five rheumatic deaths, representing a death-rate of 4 per cent.

Dosage in Five Fatal Cases.

That any of the deaths were the direct result of the use of an unusually large dose of salicylate is negatived by a consideration of the maximum doses employed in the five fatal cases. In none of them was the dose very large, as is shown in the following table: in only one was it at all large.

TABLE VI.

Showing maximum daily dose in grains given in the fatal cases of series.

Case No.	Age.	Maximum Daily Dose.
92	9	80
113	7	50
93	6	80
103	5	120
78	9	60

Influence of salicylate in five fatal cases. In two of the five fatal cases salicylate was not being taken at the time of death nor for some time previously (six weeks and twelve days respectively), while throughout the illness salicylate had been little used.

Case 92 (*v.* also notes under Table I). In ward eighteen weeks. Salicylate given for fifty days. Sixty grains daily given for first five days and repeated several times for two days at a time. For one period of three weeks 40–80 gr. daily were given. Much vomiting with and without salicylate. No salicylate given during last six weeks of life.

Case 113. Boy, aged 7 years. Polyarthritis four months in infirmary. In hospital, no symptoms but cardiac, except a few nodules appearing three days before death with rise of temperature. Heart much damaged. *Autopsy*: old mitral and tricuspid endocarditis with recent tricuspid vegetations. Diplococci in masses in tonsils. *Treatment*: In ward forty days: leeches first and nineteenth days; vomited without salicylate two days; salicylate given on twenty-seventh and twenty-eighth days only, 50 gr. daily; vomited one day.

The third fatal case was admitted *in extremis* and died very rapidly. Salicylate was given in 80 gr. doses daily, but cannot, I think, be held responsible in any way for the fatal termination.

Case 93. Girl, aged 6. In fever hospital for scarlatina thirteen weeks; discharged three days previously. Admitted extremely ill, temp. 104°. Heart's dullness very much enlarged; general pericardial and pleuropericardial friction. *Treatment*: In ward four days; leeches and ice applied to heart first day. Sodium salicylate given all four days, 80 gr. daily; vomited two days (four times). Died fourth day. *Autopsy*: mitral, aortic, and tricuspid endocarditis; pericardial effusion.

The fourth fatal case was one of severe valvular disease with adherent pericardium. The boy was very ill during the whole time (forty-two days) he was in the ward, and his cardiac symptoms gradually increased with fresh febrile attacks (probably endo- and myocarditis). He vomited with and without salicylate but not very much. At the time of death he was taking 120 gr. daily. There was some vomiting, but it does not appear that the salicylate did harm; the child getting gradually worse throughout. His cardiac condition was quite enough to account for his death. The salicylate throughout, in the doses employed, seemed powerless to improve his condition, failing to influence the temperature.

Case 103. Boy, aged 5. Rheumatic fever one year ago, not well since. Joints swollen three weeks, severe cardiac symptoms. Heart dilated three finger-breadths outside left nipple; praecordial bulging; apical presystolic and systolic. Liver three finger-breadths below costal margin. Heart gradually worse all the time, with two recrudescences of fever, lasting seven and twenty-two days. Terminal symptoms: sudden heart failure, with abdominal pain and very slight haematemesis. Died in 1½ hours. *Treatment*: leeches applied three times; venesection once; stimulants freely throughout. Salicylate at various times in doses of 46 and 96 gr. daily. For terminal fortnight none given until last four days, when 120 gr. given daily. Vomited four days (five times) on salicylate including two days of last four; without salicylate vomited four days (seven times). Autopsy: adherent pericardium; old mitral, tricuspid, and aortic endocarditis with recent aortic valvulitis; myocardium fatty.

In the fifth fatal case, it is very clear that salicylate had nothing to do with the cause of death; indeed if the drug has any power in cutting short the infection death was more due to lack of it.

Case 78. Girl, aged 9½: admitted for arthritis and slight heart disease. Given salicylate in 60 gr. daily doses for three days, then 40 gr. for six days. Vomited three days during these nine days. Tenth day, salicylate dropped and temperature went up again; fourteenth day, doubtful pericardial friction; seventeenth day, definite friction; twentieth day, very ill, 60 gr. of salicylate given daily until death; vomited twenty-first to twenty-fourth days (five vomits): twenty-sixth day, heart was better, friction gone; chorea developing; twenty-eighth day, pain in fingers; thirtieth day, temperature down to 98·6°; during thirtieth to thirty-second days seemed improving, temperature 99°; no more vomiting after twenty-fourth day; died suddenly during night on thirty-second day.

Fatal cases: Summary. None of the fatal cases died from salicylate poisoning; nor was any fatal case at any time taking a large dose of salicylate. Every case can be explained fully without supposing that salicylate had any detrimental effect on the patient: in only one case is there any possibility of the vomiting at the time of death being set up by the drug; this patient had the severest form of heart disease, and had been slowly getting worse for six weeks, with and without salicylate.

(v) *Relapses under Salicylate Treatment.*

The objection to the specific use of salicylate under this heading is that it is unsound, as the drug does not prevent relapses, particularly the development of nodules.

I have here to consider the relapses in the present series of cases, noting their relationship to the treatment, and their nature, with particular attention to nodule formation.

In investigating these points I have counted as relapses all instances with some definite rheumatic manifestation with or without pyrexia. Cases in which there was a sudden rise of temperature, subsiding very rapidly and not traced to any rheumatic cause, have been omitted. Where, however, the renewed pyrexia has been associated with fresh cardiac symptoms or increased dilatation of the heart it has been counted as a relapse.

Rheumatism is an infection which is notably prone to relapses, and particularly is this the case in the disease as seen in children.

Number of relapses. In the series of 124 cases, 17 (13·70 per cent.) showed relapse. Some showed more than one rheumatic manifestation during the relapse; one case relapsed twice. In the 17 relapses there were 23 rheumatic manifestations.

Relapses were more common in the severe cases than in the mild. Thus in the 40 cases classed as severe (severe chorea, severe heart disease, and all cases showing nodules) 9 or 22·5 per cent. relapsed; in the mild cases (84 in number) 8 or 9·52 per cent. relapsed. In the group of 27 cases classed as severe heart disease 5 (18·5 per cent.) relapsed; in the 97 others, 12 (12·3 per cent.) relapsed.

Relationship of relapse to administration of salicylate. In the 17 relapsing cases the relapse occurred in six instances when not taking salicylate, and in eleven instances when the drug was being administered. In some instances after the relapse had started, while the patient was taking no salicylate, fresh symptoms continued to develop after the drug was resumed (e.g. Case 78).

Although relapses were thus more numerous during salicylate treatment than when the drug was not being given, I do not think that we may conclude that salicylate predisposes towards relapses. The explanation lies in the fact that in nearly all cases salicylate was being given throughout the illness, and only when it could not be tolerated or where the infection was thought to be at an end was the drug omitted. If it be borne in mind that there were comparatively few opportunities for a case to relapse when not taking salicylate, that nearly one-half of the relapsing cases should come into this category seems a high proportion.

Relationship of relapse to dose employed. In Table VII the relationship of the relapses to the dose of salicylate given is shown. Where the relapse occurred

during a time when no salicylate was being taken, the case has been grouped under the maximum dose previously given.

TABLE VII.

Showing relation of relapse to dose employed at or before time of relapse.

Daily Dose. Grains.	No. showing Relapse. Taking this Dose.	No. showing Relapse. Dose as previous max.	No. of Cases given Dose. As max.	No. of Cases given Dose. During Treatment.
1–50	5	2	8	124
51–100	4	3	38	116
101–150	0	0	36	78
151–200	1	1	22	42
201–250	1	0	4	20
251–300	0	0	12	16
301–350	0	0	2	4
351–400	0	0	2	2

The figures shown in Table VII suggest that the cases treated with larger doses enjoy a considerable immunity to relapses; 14 out of 17 relapsing cases developing their relapse on or after doses of not more than 100 gr. of salicylate per diem.

Nature of relapse: Nodules. The nature of the rheumatic manifestations (23 in number) which developed in the 17 relapsing cases of the series is shown in Table VIII.

TABLE VIII.

Nature of relapses in 17 relapsing cases.

Nature of Relapse.	With Salicylate.	Without Salicylate.	Total.
Tonsillitis . . .	4	0	4
Arthritis and joint pains . . .	3	2	5
Chorea . . .	2	1	3
Nodules . . .	4	1	5
Endo- or myocarditis .	1	3	4
Pericarditis . .	0	1	1
Rash	1	0	1

The series of cases under examination were, it must be remembered, freely treated with salicylate. In every case the drug was given in doses thought to be sufficient to subdue the activity of the infection or as large as could be tolerated. Thus it becomes most interesting to observe that the two rheumatic manifestations which figure most frequently in relapses are arthritis and nodules. This is significant, since it suggests that salicylate does not fail to prevent nodule formation in any peculiar way. Arthritis is generally acknowledged to be the rheumatic symptom most clearly controlled by salicylate: it is quickly relieved, and, from the cessation of the involvement of fresh joints which is so characteristic of rheumatic arthritis, it is certainly tenable that salicylate tends to prevent arthritis.

Nodule formation. The above fact is suggestive, but the objection that salicylate does not influence rheumatic nodules, and particularly does not prevent their development, must be examined more closely.

The rheumatic nodule is generally regarded as the response of the tissues to the local presence of rheumatic organisms. Coombs's histological researches have shown that the subcutaneous nodule is essentially the same in origin and evolution as the microscopical submiliary nodules found in all organs infected by the rheumatic organism. The subcutaneous nodules may be regarded, as Coombs (1) has suggested from their histological characters and distribution, as the results of bacterial thrombosis of end-arteries. If this be so, their development may signify one of two things. Either, first, a general rheumatic bacteriaemia, suggested by the nodules being widely distributed and their development associated with fever, active carditis, &c.; or merely that a mass of organisms had got into the circulation (possibly from a valve segment) and acted as an embolus. This latter would be suggested where the distribution of nodules was strictly localized and unaccompanied by fresh fever or other signs of active rheumatic infection.

Now the argument about the influence of salicylate on nodules is threefold. In the first place, it is said that the drug does not help their disappearance. In answer to this it may be submitted that the life of a rheumatic nodule is variable in length. We are not able to foretell how long a nodule may be expected to persist. Their disappearance or persistence is presumably a sign of the resistance of the patient and due to the activity of the rheumatic infection. We cannot expect salicylate to absorb the nodule; and thus, if it could be shown by other means that salicylate tended to cut short the activity of the infection, I should be content to assume that the drug was doing all that an anti-rheumatic drug could be expected to do to hasten the disappearance of the nodule.

Secondly, it is held that salicylate treatment does not prevent nodule formation. We are not, however, able to foretell, except in the roughest way, what cases will develop nodules, and therefore this matter can also only be settled by an examination of the anti-rheumatic action of salicylate. If the drug tends to cut short the infection we must assume that, speaking generally, it tends to prevent nodule formation.

Lastly, and this is the important point, it is held that nodules may develop under treatment by salicylate, even in full doses. This is undoubtedly true, and an instance will be quoted immediately, but examination in detail brings out an interesting point concerning such cases.

In the present series nodules developed during the patient's treatment in hospital in five instances. These are now examined in order to trace the relationship of the nodule formation to salicylate treatment.

In three cases it is evident that the development of the nodules cannot be regarded as a failure of salicylate treatment, as the drug had been given either in very small doses or for a very short time.

1. *Case* 113. In ward forty days. Salicylate given only on two days (twenty-seventh and twenty-eighth) in doses of 50 gr. daily. Nodules developed three days before death with renewed fever.

2. *Case* 91. A few nodules developed fourth day in ward; temperature had not reached normal; 100 grains of salicylate given daily.

3. *Case* 118. A few nodules developed with increased fever during fifth week in ward. Child did not take salicylate well; had never more than 50 gr. daily, and that for not more than three days at a time. Temperature never satisfactory. Before nodules developed had been taking quinine for six days and aspirin (9 gr. daily) for four days.

In the fourth case salicylate was being given in what was deemed to be a sufficient amount, although the temperature was not quite satisfactory. The interesting points in this case are that with the nodule arthritis developed, and that there was no rise of temperature or fresh carditis at the time of the relapse; suggesting that the infection was to some considerable extent under control and that the drug did not here fail in any peculiar way as regards nodule prevention.

4. *Case* 80. Under treatment for chorea for fourteen days on 80 gr. of salicylate daily. Temperature swinging, but not reaching 100° at night. At end of second week chorea got worse and dose raised to 100 gr. A week later right knee became painful and one nodule developed by the right patella. No alteration in temperature.

The fifth and last case is of particular interest, as nodules developed while large doses of salicylate were being taken.

5. *Case* 90. Admitted for slight heart disease, atonic chorea with aphasia and a very large number of nodules, many large, including spinous processes of vertebrae, iliac spines, sacrum, scapulae, &c. Salicylate increased to 250 gr. daily. At end of fourth week, after one week on this dose, fresh nodules appeared on left elbow and hand during three days and then rapidly disappeared. Dose increased to 300 gr. Temperature normal or subnormal during these days and for previous week; no increase of pulse-rate or size of heart; no other rheumatic manifestations. Child did well, heart improved throughout; aphasia six weeks, walked twelfth week; discharged thirteenth week with only two remaining nodules on right patella.

In this case, without entering into the question of the utility of such large doses of salicylate in an afebrile case of chorea, it cannot be denied that the result was most satisfactory. With regard to the development of the nodules it is notable that there was no sort of renewal of a general infection, the signs of activity being seen only in connexion with the nodules; and this suggests that the infection was under satisfactory control. Further, the very localized distribution of the fresh nodules would be adequately explained by embolism, and if so, would not signify a fresh activity of the infection. The disappearance of the fresh nodules was rapid. These facts then suggest, first, that the infection was under very good control; secondly, that the appearance of the nodules did

not necessarily imply any fresh activity of the infection. The first point appears to me certain, the second probable.

Relapses under salicylate: Summary. The majority (82 per cent.) of relapses occur in such cases as have not been treated on larger doses of salicylate than 100 gr. daily.

Generally speaking, nodules are not a more frequent form of relapse than arthritis. Where they develop on large doses of salicylate they do not seem of serious significance, and may probably sometimes be explained without presuming any fresh activity on the part of the infection.

General Conclusions.

I am not here concerned with the truth of the theory that salicylate diminishes the activity of the rheumatic infection. I have examined certain objections to this view and submit the following conclusions on the issues raised:

1. The objection that the larger doses of salicylate do not imply increased absorption of the drug is without foundation.

2. The objection that the larger doses are too prone to produce vomiting to be of value is only partially true. The production of vomiting is more a matter of the type of case under treatment and the methods of administration than the size of the dose employed. The vomiting produced in severe cardiac cases must necessarily be a limitation to any anti-rheumatic action which the drug may possess in rheumatic carditis.

3. The objection that large doses are too prone to produce acid intoxication to be of value is only partially true. The method of administration is of more importance than the size of the dose.

4. The objection that the larger doses are dangerous and tend to increase fatalities is not supported by the series of cases examined. It is again a question of knowing how and when to use the drug.

5. The objection that the specific use of salicylate is unsound, as relapses, particularly of nodules, are not prevented, is not well supported by the series of cases examined. Most of the relapses occurred on or after small doses or a short period of administration of the drug; cases taking large doses showing some immunity to relapses. Nodules are not generally more commonly found in relapses than are other manifestations; and where they develop under large doses it seems that they signify little, if any, fresh activity on the part of the infection.

REFERENCES.

1. Coombs, 'Rheumatic Infection from the Histological Point of View,' *St. Mary's Hosp. Gazette*, Lond., 1913, ii. 22. (This paper contains a useful summary of author's work.)

2. Langmead, 'Salicylate Poisoning in Children,' *Lancet*, Lond., 1906, i. 1822.

3. Lees, *Brit. Med. Journ.*, 1912, ii. 930.

4. Miller, 'Latent Chorea,' *Lancet*, Lond., 1909, ii. 1808.

5. Poynton, 'Rheumatism in Childhood,' *Practitioner*, Lond., 1913, xc, ii. 412.

6. The most important discussions on the salicylate treatment of rheumatism in England of recent years are recorded in the following publications:

1908, *Proc. Roy. Soc. Med.*, Lond. (Therap. and Pharmac. Sect.), 65.
1909, *Ibid.*, 31.
1911, *Med. Soc. Trans.*, Lond., xxxiv. 360.
1912, *Brit. Med. Journ.*, 1912, ii. 929.